Advances in HETEROCYCLIC CHEMISTRY

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Preface

The continuing rapid advance of knowledge in the heterocyclic field explains the publication of the present book so rapidly after the first volume of the series. The reviews in these volumes fall into two categories—those dealing with a particular ring system or group of ring systems (isoxazoles, selenazoles, oxazines, quinoxalines, three-membered rings with two hetero atoms) and those covering a type of reaction or a chemical or physical property. Previous publications on heterocyclic chemistry have been mainly concerned with the first type, i.e., all the topics mentioned (except the novel three-membered rings). It is our policy to make reference to previous reviews and then to concentrate on the subsequent literature, giving older references only for special reasons.

Reviews dealing with a specific reaction or property from the heterocyclic point of view have been rarer—tautomerism (continued from Volume 1), free radical substitution, metal catalysts and pyridines, acid-catalyzed polymerization of pyrroles, and diazomethane reactions have been covered in this volume.

It is planned to publish Volumes 3 and 4 of this series early and late in 1964, respectively. Suggestions for contributions to further volumes will be welcomed; they should be in the form of a short synopsis.

I would like to thank the authors of the reviews for their cooperation, the members of the Editorial Board, the publishers, and, especially, the assistant editors Dr. A. J. Boulton and Dr. J. M. Lagowski.

A. R. KATRITZKY

Norwich, England
June 1963

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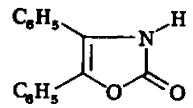
In Volume 1, in the chapters on Prototropic Tautomerism by A. R. Katritzky and J. M. Lagowski,

p. 333, formula (*53*) should be



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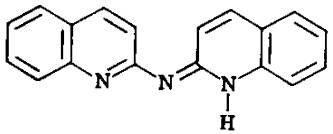

Prototropic Tautomerism of Heteroaromatic Compounds: III. Five-Membered Rings and One Hetero Atom*

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AND

J. M. LAGOWSKI

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The most important potentially tautomeric thiophenes and furans are those carrying hydroxyl, mercapto, and amino groups. In these compounds a prototropic shift can occur between the functional group

*The first two chapters in this volume conclude the series of four articles on prototropic tautomerism; the first two articles appeared in Volume 1. Cross references to these articles include, for easy identification, the roman numeral given in the title.

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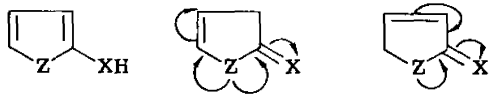
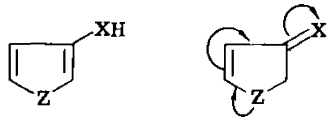
and a ring carbon atom, cf. type *ii* described in Volume 1, Section I,A, of article I by Katritzky and Lagowski. A single functional group in the α-position gives rise to three possible tautomeric structures, **1–3**, whereas two structures, **4** and **5**, are possible with one functional group in the β-position. Similar structures are possible for the analogous pyrroles, but pyrroles which do not carry a substituent on the hetero nitrogen atom can undergo additional types of tautomerism (see later). The proportion of the various forms present at equilibrium is dependent upon their relative stability. Forms **1** and **4** are "aromatic," and, since the aromatic stabilization decreases in the order thiophene > pyrrole > furan, forms of this type would be expected to be the most favored for thiophenes. The nonaromatic forms are, however, also mesomeric as indicated by curly arrows in **2**, **3**, and **5**.



[1] [2] [3]



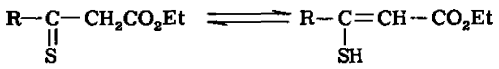
[4] [5]

Systems **2** and **3** are cross-conjugated, but **5** is not, and it might have been expected that α-substituted compounds would be more prone to exist in the aromatic form **1** than the β-compounds to exist as **4**. From the limited evidence available, the reverse appears to be the case. When the hetero atom is not a very strong electron donor, i.e., Z = S or O, structure **3** would be expected to be relatively more stable than **2**, and this is supported by the evidence available. When Z = NR, the difference in the stabilities of **2** and **3** could be smaller.

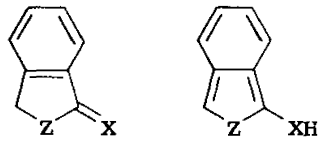
The nature of the substituent group X plays an important role in determining the relative stability of the various tautomeric forms. In aliphatic systems the tendency of :C=Ċ—XH to become :CH—Ċ=X increases markedly in the order $X = CH_2 < NH < O$, and certainly hydroxy compounds show less inclination to exist as such than do amino compounds. The position of S in this series is not completely

clear (see discussion in Section III of article II, Volume 1); however, the thione-thiol equilibrium **6** ⇌ **7** appears to be more in favor of **7** than in the case of the corresponding keto-enol equilibrium.[1] In agreement with this contention, mercaptothiophenes are more stable than the hydroxythiophenes (discussed later).

Electron-withdrawing substituents stabilize the aromatic forms **1** and **4**, as would be expected, by acting as an "electron sink" and by forming intramolecular hydrogen bonds with the XH group when this is sterically possible. On the other hand, a benzene ring fused in the 3,4-position greatly stabilizes **8** as compared to **9**. The effect of a benzene ring fused in the 4,5-position is smaller, but probably also causes some preferential stabilization of the nonaromatic forms corresponding to **2** and **5**.



[6] [7]



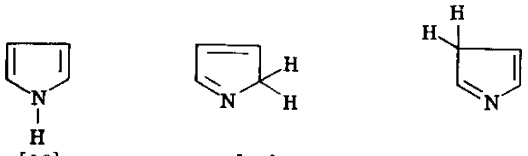
[8] [9]

I. Tautomerism of Pyrroles Not Involving the Functional Group

The tautomeric forms **11** and **12**, called pyrrolenines, have often been postulated for pyrrole (**10**), but there is no conclusive evidence for their existence.[2] The report[3] that two isomers exist as the pyrrolenine forms **13** and **14** (Ar = 3,4-dimethoxyphenyl) must be regarded with considerable doubt.

Chemical evidence led to the conclusion that the conjugate acids of pyrrole probably exist predominantly as **16** or **17** rather than as **15**.[2,4,5] Although infrared spectra were initially interpreted on the

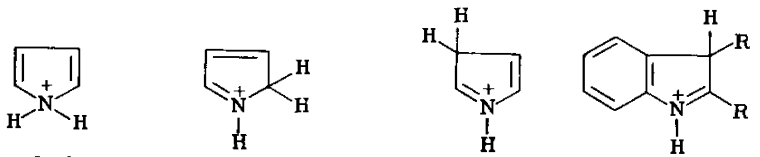
[1] Z. Reyes and R. M. Silverstein, *J. Am. Chem. Soc.* **80**, 6367 (1958).
[2] A. Treibs and G. Fritz, *Ann. Chem. Liebigs* **611**, 162 (1958).
[3] D. A. Guthrie, A. W. Frank, and C. B. Purves, *Can. J. Chem.* **33**, 729 (1955).
[4] A. Treibs and K. H. Michl, *Ann. Chem. Liebigs* **577**, 129 (1952).
[5] A. Treibs and A. Ohorodnik, *Ann. Chem. Liebigs* **611**, 139 (1958).



[10] [11] [12]

[13] [14]

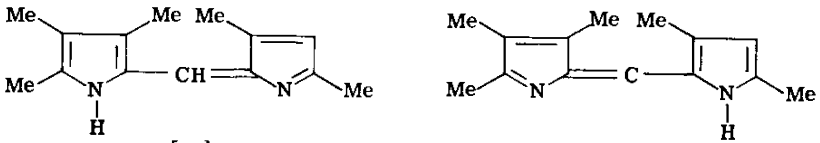
basis of structure **15**,[6] nuclear magnetic resonance spectra later proved that structures of type **16** were favored in solution.[7] Similarly, ultraviolet[8] and nuclear magnetic resonance spectra[9] and basicity measurements[9a] show that indole cations are formed by protonation at the



[15] [16] [17] [18]

β-position to give **18**, substantiating the postulation which had been offered earlier on theoretical grounds.[5]

Dipyrromethenes rapidly exchange the hydrogen atom attached to nitrogen, and the two isomers of unsymmetrical compounds (e.g., **19** and **20**) cannot be separately isolated.[10] Dipyrromethenes form meso-



[19] [20]

[6] E. Bullock, *Can. J. Chem.* **36**, 1686 (1958).
[7] R. J. Abraham, E. Bullock, and S. S. Mitra, *Can. J. Chem.* **37**, 1859 (1959).
[8] M. J. Kamlet and J. C. Dacons, *J. Org. Chem.* **26**, 220 (1961).
[9] R. L. Hinnar and J. Lang, *Tetrahedron Letters* No. 21, 12 (1960).
[9a] G. Berti, A. Da Settimo, and D. Segnini, *Gazz. chim. ital.* **91**, 571 (1961).
[10] H. Fischer and B. Walach, *Ann. Chem. Liebigs* **450**, 109 (1926).

[21] [22]

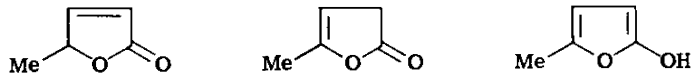
meric cations (cf. **21**) by proton addition at nitrogen,[5] whereas olefinic derivatives such as **22** undergo proton addition on carbon.

II. Compounds with a Potential Hydroxyl Group

Heterocyclic compounds carrying hydroxyl groups may be compared with phenols. Thomson[11] has reviewed the tautomeric behavior of phenols; often both tautomeric forms of polycyclic compounds such as naphthols can be isolated. Early work on hydroxythiophenes and -furans was also reviewed by Thomson,[11] but until recently their chemistry has been in a somewhat confused state. A pattern is now beginning to emerge, at least for the α-substituted compounds, which appear to exist as Δ^3-oxo derivatives and to attain equilibrium slowly with the corresponding Δ^4-oxo forms. For the α-hydroxy compounds, the equilibrium generally favors the Δ^3-oxo form.

A. Hydroxyfurans

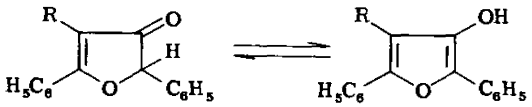
Unsaturated γ-lactones, e.g., α- (**23**) and β-angelica lactone (**24**), are well known. Compounds **23** and **24** are both converted by alkaline catalysts into an equilibrium mixture in which **23** predominates, the amount of the hydroxy form (**25**) present at equilibrium being exceedingly small. True α-hydroxyfurans are unknown, and, although the preparation of both α- and β-hydroxyfurans has been reported,[12,13] these claims have often been refuted (see, e.g., reference 14).



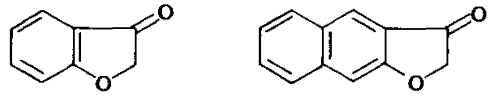
[23] [24] [25]

[11] R. H. Thomson, *Quart. Revs. (London)* **10**, 27 (1956).
[12] H. H. Hodgson and R. R. Davies, *J. Chem. Soc.* p. 806 (1939).
[13] H. H. Hodgson and R. R. Davies, *J. Chem. Soc.* p. 1013 (1939).
[14] M. P. Cava, C. L. Wilson, and C. J. Williams, *J. Am. Chem. Soc.* **78**, 2303 (1956).

Very little is known concerning the simple, monocyclic 3-hydroxyfurans (cf. reference 15). Both the oxo and hydroxy forms of the substituted 3-hydroxyfurans **26** and **27** (R = H, C_6H_5) have been isolated,[16,17] but the individual tautomers slowly undergo interconversion. The enol forms give a positive reaction with ferric chloride, react rapidly with bromine, and form a peroxide with oxygen. From chemical evidence, the benzo derivatives of 3-hydroxyfuran, **28**[18] and **29**,[19] appear to exist predominantly in the oxo form, and this is further supported by ultraviolet spectral data.[20] Stefanye and Howard[21]



[26] [27]

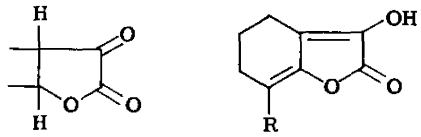


[28] [29]

concluded from infrared spectroscopic data that 5,7-dichloro-3-hydroxybenzofuran exists in the oxo form, but that the hydroxy form of its 2-(5′,7′-dichlorobenzofuryl) derivative, i.e., 3-hydroxy-5,5′,7,7′-tetrachloro-2,3′-bibenzofuran, apparently predominates.

B. Potential Dihydroxyfurans

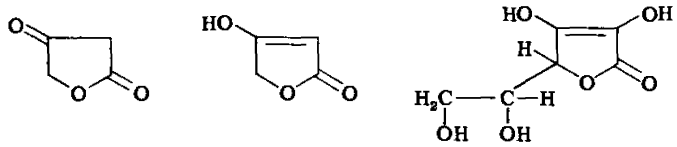
α-Keto-γ-lactones appear to exist in the dioxo form **30**,[22] but enolization can occur when this leads to extended conjugation. The enol forms of **31** (R = C_6H_5) and **31** (R = H) have been shown to be predominant by chemical evidence[23] and by infrared spectral data,[24]



[30] [31]

respectively.

Tetronic acids exist predominantly in the dioxo form (**32**) in solvents of low polarity, while the existence of the monoenol form (**33**) has been established in other solvents by infrared[25] and ultraviolet spectral comparisons[26] and from dipole moment data.[27] Haynes and Plimmer[27a] have recently reviewed the structure of these compounds [see also reference 28(a)], and the tautomerism of vitamin A (**34**), which has a related structure, has also been surveyed.[28(b)] Analogous compounds carrying an amino group in the 3-position are also known.[28(c)]

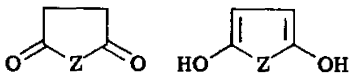


[32] [33] [34]

Succinic anhydride (**35**, Z = O) can theoretically tautomerize to **36**, but all the evidence indicates that it exists overwhelmingly as **35**; for example, the infrared spectrum shows ν C=O bands.[29]

[15] E. Votoček and S. Malachta, *Collection Czechoslov. Chem. Communs.* **4**, 87 (1932).
[16] E. P. Kohler, F. H. Westheimer, and M. Tishler, *J. Am. Chem. Soc.* **58**, 264 (1936).
[17] E. P. Kohler and D. W. Woodward, *J. Am. Chem. Soc.* **58**, 1933 (1936).
[18] K. v. Auwers and E. Auffenberg, *Ber. deut. chem. Ges.* **52**, 92 (1919).
[19] P. Emmott and R. Livingstone, *J. Chem. Soc.* p. 4629 (1958).
[20] Mme. Ramart-Lucas and M. van Cowenbergh, *Bull. soc. chim. France* p. 1381 (1935).
[21] D. Stefanye and W. L. Howard, *J. Org. Chem.* **20**, 813 (1955).
[22] Pl. A. Plattner and L. M. Jampolsky, *Helv. Chim. Acta* **26**, 687 (1943).
[23] W. E. Bachmann, G. I. Fujimoto, and L. B. Wick, *J. Am. Chem. Soc.* **72**, 1995 (1950).
[24] L. Mangoni and M. Belardini, *Ann. chim. (Rome)* **50**, 322 (1960).
[25] L. A. Duncanson, *J. Chem. Soc.* p. 1207 (1953).
[26] E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* p. 1419 (1949).
[27] W. D. Kumler, *J. Am. Chem. Soc.* **62**, 3292 (1940).
[27a] L. J. Haynes and J. R. Plimmer, *Quart. Revs. (London)* **14**, 292 (1960).
[28] H. von Euler and B. Eistert, "Chemie und Biochemie der Reduktone und Reduktonate," (a) p. 159, (b) p. 185, (c) p. 261. F. Enke, Stuttgart, Germany, 1957.
[29] H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, "Infrared Determination of Organic Structures." D. Van Nostrand, New York, 1949.

Infrared and nuclear magnetic resonance spectral evidence led Kendall and Hajos[30] to conclude that furan-3,4-dione (**37**) exists as such, which is surprising since cyclic α-diketones with five-membered rings are usually monoenolized. The 2,5-dicarbethoxy derivative **38** was earlier stated to exist in the dihydroxy form.[31]



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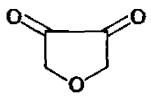

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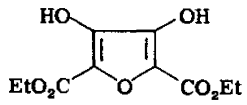
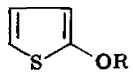


[38]

C. α-Hydroxythiophenes

The infrared spectrum of 2-hydroxythiophene was originally interpreted as showing both νOH and νC=O peaks indicating that it exists as a mixture of the hydroxy form **39** (R = H) and at least one of the oxo forms, **40** and/or **41**.[32] The ultraviolet spectrum of 2-hydroxythiophene is different from that of the corresponding methyl ether (**39**, R = Me) suggesting the presence of the chromophore contained in structure **40**. The facts that this compound gives a positive



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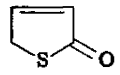

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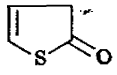


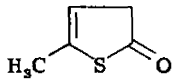
[41]

color test with ferric chloride, is a weak acid, and undergoes reactions characteristic of a phenolic hydroxyl group have been advanced as further evidence for the presence of the hydroxy form.[32] The infrared

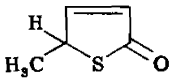
[30] E. C. Kendall and Z. G. Hajos, *J. Am. Chem. Soc.* **82**, 3219 (1960).
[31] W. H. Hoehn, *Iowa State Coll. J. Sci.* **11**, 66 (1936); *Chem. Abstr.* **31**, 1800 (1937).
[32] C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.* **72**, 5543 (1950).

spectrum of 5-phenyl-2-hydroxythiophene measured in chloroform solution shows a C=O absorption band, but its ultraviolet spectrum in ethanol is rather similar to that of the corresponding 2-methoxy derivative. Comparison of the ultraviolet spectra was complicated by a spontaneous oxidation of the latter compound. The ultraviolet spectrum measured in chloroform or isooctane did not correspond to that obtained in ethanol. Chemical evidence was also considered to support a mobile keto-enol tautomeric equilibrium.[33]

The foregoing conclusions must now be modified on the basis of a recent, detailed investigation of the tautomerism of 2-hydroxy-5-methylthiophene by Gronowitz and Hoffman[34] using nuclear magnetic resonance and infrared spectroscopy. Compounds **42** and **43** form an equilibrium mixture containing 85% of **43**. However, equilibrium is attained slowly, and **42** can be obtained essentially pure by dissolving the mixture in a base and precipitating with acid, whereas almost pure **43** can be isolated by distillation. The effect of the methyl group in stabilizing structure **42** is illustrated by the fact that 2-hydroxythiophene itself exists essentially completely as **40**.[34]



[42]



[43]

2-Hydroxythianaphthene has been isolated in two forms,[35] and it has been suggested that these may be the individual keto and enol tautomers.[11] A reinvestigation of this system using modern techniques would be welcome.

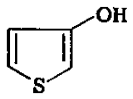
D. β-Hydroxythiophenes

The infrared spectrum of 3-hydroxythiophene has been interpreted by Ford and Mackay[36] to show that it exists as a mixture of both the hydroxy (**44**) and the oxo forms (**45**). 5-Phenyl-3-hydroxythiophene apparently behaves similarly to the 2-hydroxy isomer, the ultraviolet

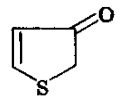
[33] A. I. Kosak, R. J. F. Palchak, W. A. Steele, and C. M. Selwitz, *J. Am. Chem. Soc.* **76**, 4450 (1954).
[34] S. Gronowitz and R. A. Hoffman, *Arkiv Kemi* **15**, 499 (1960).
[35] C. Marschalk, *J. prakt. Chem.* **88**, 227 (1913).
[36] M. C. Ford and D. Mackay, *J. Chem. Soc.* p. 4985 (1956).

spectrum measured in ethanol suggesting that it exists in the hydroxy form, whereas that determined in chloroform indicates that one of the oxo forms predominates.[33] An alkoxycarbonyl group in the 2-position of the thiophene nucleus probably stabilizes a hydroxyl group in the 3-position (cf. reference 37).

In 1920, Auwers and Thies[38] suggested that 3-hydroxythianaphthene

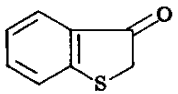


[44]

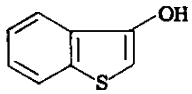


[45]

might exist as **46** in the solid state, but partly as **47** in alcoholic solution. These conclusions appear to be supported in part by more recent work,[39] although infrared spectral data indicate that the oxo



[46]



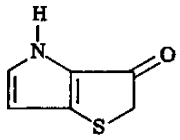
[47]

form (**46**) greatly predominates in both chloroform and carbon disulfide solutions.[40]

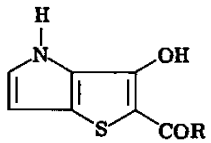
Snyder and his co-workers[41,42] assigned structures **48** and **49** to these β-hydroxythiophene derivatives on the basis of chemical evidence and infrared and nuclear magnetic resonance spectral data. Infrared and nuclear magnetic resonance spectra further indicate that compounds of type **49** exist as dimers, probably hydrogen bonded, when $R = OC_2H_5$ or CH_3, but as monomeric enols when $R = H$.[43]

[37] H. Fiesselmann and P. Schipprak, *Chem. Ber.* **89**, 1897 (1956).
[38] K. v. Auwers and W. Thies, *Ber. deut. chem. Ges.* **53**, 2285 (1920).
[39] F. Kröhnke, *Chem. Ber.* **92**, cxiv (1959).
[40] S. J. Holt, A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.* p. 1217 (1958).
[41] W. Carpenter and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 2592 (1960).
[42] D. S. Matteson and H. R. Snyder, *J. Org. Chem.* **22**, 1500 (1957).
[43] R. J. Tuite, A. D. Josey, and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 4360 (1960).

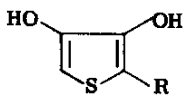
On the basis of chemical evidence, Swiss investigators have postulated that 3,4-dihydroxythiophenes exist as diols, i.e., as **50**.[44,45]



[48]



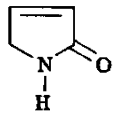
[49]



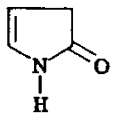
[50]

E. α-Hydroxypyrroles

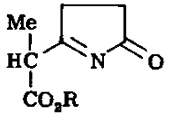
2-Hydroxypyrroles are thought to exist in oxo forms such as **51** or **52**; structure **53** illustrates a third possible oxo form.[46] Chemical evidence for tautomerism in the hydroxypyrroles has been reviewed by Fischer and Orth.[47] Since 2-hydroxypyrrole itself is unstable and



[51]



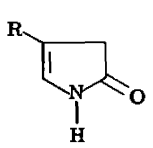
[52]



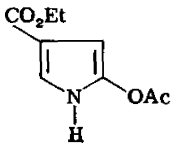
[53]

rapidly resinifies, studies have been confined to some of its more stable derivatives. The ultraviolet spectrum of **54** ($R = CO_2Et$) is different from that of **55**, and **54** ($R = CO_2Et$) does not give a positive test with ferric chloride,[48,49] which led to its formulation as shown. On the basis of their infrared (and ultraviolet) spectra, compounds **56** ($R = H$),[50] **56** ($R = Ac$),[50] and **57**[51] must exist in oxo forms since they exhibit ν C=O absorption bands: **56** ($R = H$) at 5.95μ (1681 cm^{-1}), **57** at 5.90μ (1695 cm^{-1}), and **56** ($R = Ac$) two bands at 5.87 and 5.95μ (1704 and 1681 cm^{-1}). Proton resonance

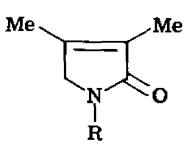
[44] P. Karrer and F. Kehrer, *Helv. Chim. Acta* **27**, 142 (1944).
[45] P. Karrer, R. Keller, and E. Usteri, *Helv. Chim. Acta* **27**, 237 (1944).
[46] H. Lapin and A. Horeau, *Bull. soc. chim. France* p. 1703 (1960).
[47] H. Fischer and H. Orth, "Die Chemie des Pyrrols." Vol. I, p. 124. Akademische Verlag., Leipzig, 1934.
[48] C. A. Grob and P. Ankli, *Helv. Chim. Acta* **32**, 2010 (1949).
[49] C. A. Grob and P. Ankli, *Helv. Chim. Acta* **32**, 2023 (1949).
[50] H. Plieninger and M. Decker, *Ann. Chem. Liebigs* **598**, 198 (1956).
[51] K. E. Schulte, J. Reisch, and R. Hobl, *Arch. Pharm.* **293**, 687 (1960).



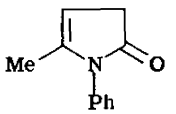
[54]



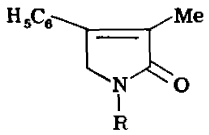
[55]



[56]



[57]



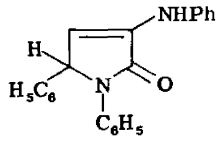
[58]

spectra confirm structure **56** (R = H).[51a] The Δ^4-structure was assigned to **57** because it added water reversibly, and this is considered to be a characteristic reaction of Δ^4-pyrrolones,[52] whereas the Δ^3-structure was assigned to **56** (R = H) because the ultraviolet spectrum appeared to be of the crotonic acid type.[50] Ultraviolet spectra suggested, and nuclear magnetic resonance spectra proved, that **58** (R = H, OH) should be assigned the Δ^3-structure shown.[53]

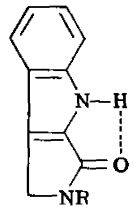
The tautomeric behavior of compounds of type **59** has been discussed by Meyer and Vaughan.[54] An intramolecularly hydrogen-bonded oxo structure has been assigned to **60** on the basis of its infrared spectrum,[55] whereas unambiguous chemical evidence, i.e., ozonolysis to succimide, confirmed the isolation of **61** in the oxo form.[56]

The foregoing results may be summarized as follows: potential α-hydroxypyrroles exist as pyrrolones. Substituents in the 3-position and in the 5-position favor the Δ^3- and the Δ^4-pyrrolone structure, respectively, as is to be expected. For 3,4,5-trisubstituted compounds, such as **61b**, the Δ^3-structure appears to be preferred.[51a] An electron-

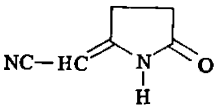
[51a] H. Plieninger, H. Bauer, and A. R. Katritzky, *Ann. Chem. Liebigs* **654**, 165 (1962).
[52] K. E. Schulte and J. Reisch, *Arch. Pharm.* **292**, 51 (1959).
[53] J. A. Moore and J. Binkert, *J. Am. Chem. Soc.* **81**, 6029 (1959).
[54] W. L. Meyer and W. R. Vaughan, *J. Org. Chem.* **22**, 1565 (1957).
[55] P. L. Southwick and R. J. Owellen, *J. Org. Chem.* **25**, 1133 (1960).
[56] J. A. Elvidge, J. S. Fitt, and R. P. Linstead, *J. Chem. Soc.* p. 235 (1956).



[59]

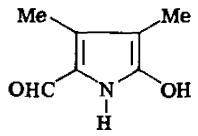


[60]

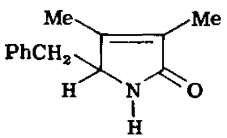


[61]

accepting substituent in the 4-position favors the Δ^4-pyrrolone structure, because conjugation between the substituent and the cyclic nitrogen atom is then possible. An electron-accepting substituent in the 5-position might be expected to stabilize the hydroxypyrrole form, because only then is extended conjugation possible in the molecule: the aldehyde **61a** does, indeed, exist as shown on proton resonance spectral evidence.[51a]



[61a]

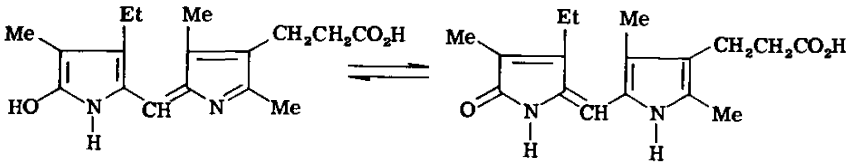


[61b]

Interesting tautomeric possibilities exist in the xanthobilirubic acid series (cf. reference 57) which can be illustrated by the equilibrium **62** ⇌ **63**. More complex examples of the same type are found among the linear tetrapyrrole pigments—the bilenes, bilidienes, and bilitrienes—and have been discussed by Stevens.[58] Relatively little evidence is available concerning the fine structure of these compounds, although the formation of complexes has been advanced as evidence for the oxo structure in some cases.[59]

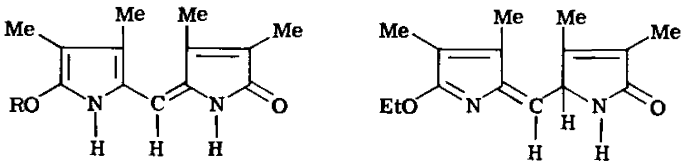
Recently, the tautomerism of 5,5′-dihydroxydipyrromethanes and the corresponding 5-hydroxy-5′-ethoxy derivatives has been investi-

[57] H. Fischer, T. Yoshioka, and P. Hartmann, *Z. physiol. Chem.* **212**, 146 (1932).
[58] T. S. Stevens, *in* "Chemistry of the Carbon Compounds" (E. H. Rodd, ed.), Vol. IVB, p. 1111 ff. Elsevier, Amsterdam, 1959.
[59] K. W. Bentley, "The Natural Pigments," p. 162. Interscience, New York, 1960.

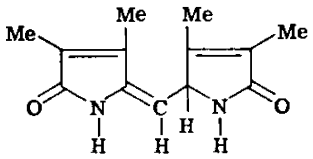


[62] [63]

gated.[51a] Two forms were isolated in each class which were assigned structures **63a** (R = H, Et), **63b**, and **63c** on the basis of ultraviolet, infrared, and proton resonance spectra.



[63a] [63b]



[63c]

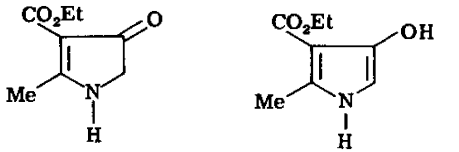
Gray and his associates[59a] have discussed equilibria involving the side chains of tetrapyrrole bile pigments.

F. β-Hydroxypyrroles

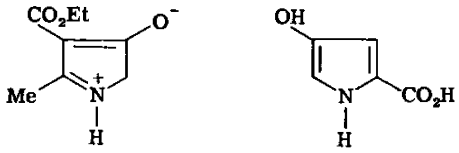
Less is known about the β-hydroxypyrroles than about the isomeric α-hydroxy compounds. Originally ethyl 4-hydroxy-2-methylpyrrole-3-carboxylate was suggested, on the basis of chemical evidence, to exist as a mixture of the oxo and hydroxy forms, **64** and **65**, respectively.[60]

[59a] C. H. Gray, A. Kulczycka, and D. C. Nicholson, *J. Chem. Soc.* pp. 2268, 2276 (1961).
[60] E. Benary and B. Silbermann, *Ber. deut. chem. Ges.* **46**, 1363 (1913).

The chemical reactions of this compound were recently reconsidered, and both structures **64** and **65** were "rejected" in favor of the zwitterion formulation **66**, which is supported by the presence of a band at 3.1μ (3226 cm^{-1}) in the infrared spectrum[61] and is merely an alternative canonical form of **64**. On the other hand, the ultraviolet spectrum of 4-hydroxypyrrole-2-carboxylic acid (**67**) resembles that of its ethyl ether, possibly indicating that the 2-acid exists in the hydroxy form.[62]



[64] [65]

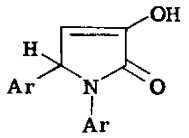


[66] [67]

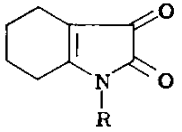
G. Poly-oxo- and -hydroxy-pyrroles and -indoles

Infrared and ultraviolet spectral data indicate that 1,5-diarylpyrrolidine-2,3-diones exist in the monooxo form **68**.[63] Chemical evidence was advanced for a tautomeric equilibrium between **69** and **70**,[64] and later spectroscopic work showed that **70** was the predominant form.[65] Compounds of type **71** were formulated, without experimental evidence, in the oxo-imino form,[64] although the tendency for C=NR → C—NHR is usually greater than that for C=O → C—OH in analogous cases.

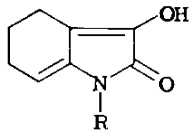
[61] A. Treibs and A. Ohorodnik, *Ann. Chem. Liebigs* **611**, 149 (1958).
[62] R. Kuhn and G. Osswald, *Chem. Ber.* **89**, 1423 (1956).
[63] W. R. Vaughan and L. R. Peters, *J. Org. Chem.* **18**, 382 (1953).
[64] L. Horwitz, *J. Am. Chem. Soc.* **75**, 4060 (1953).
[65] D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.* p. 876 (1959).



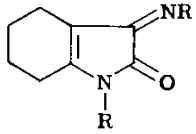
[68]



[69]



[70]

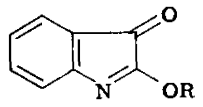


[71]

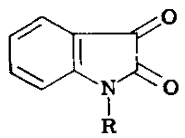
In 1882 Baeyer and Oekonomides[66] advanced formula **72** (R = H) for isatin on chemical grounds, but shortly thereafter the dioxo structure **73** (R = H) was proposed since the ultraviolet spectrum of isatin resembled that of the N—Me derivative (**73**, R = Me) and not that of the O—Me derivative (**72**, R = Me).[67] It was later shown, despite a conflicting report,[68] that the ultraviolet spectrum of isatin is very similar to the spectra of *both* the O— and N—Me derivatives[69–71]; the early investigators had failed to take into consideration the facile decomposition of the O—Me derivative. Although isolation of the separate tautomers of isatin has been reported,[72] these claims were disproved.[71] A first attempt to determine the position of the mobile hydrogen atom using X-ray crystallographic techniques was inconclusive,[73] but later X-ray work,[74] dipole moment data,[75] and especially the infrared spectrum[76] demonstrated the correctness of the

[66] A. v. Baeyer and S. Oekonomides, *Ber. deut. chem. Ges.* **15**, 2093 (1882).
[67] W. N. Hartley and J. J. Dobbie, *J. Chem. Soc.* **75**, 640 (1899).
[68] J. Dabrowski and L. Marchlewski, *Bull. soc. chim. France* **53**, 946 (1933).
[69] R. A. Morton and E. Rogers, *J. Chem. Soc.* **127**, 2698 (1925).
[70] R. G. Ault, E. L. Hirst, and R. A. Morton, *J. Chem. Soc.* p. 1653 (1935).
[71] A. Hantzsch, *Ber. deut. chem. Ges.* **54**, 1221 (1921).
[72] G. Heller, *Ber. deut. chem. Ges.* **53**, 1545 (1920).
[73] E. G. Cox, T. H. Goodwin, and A. I. Wagstaff, *Proc. Roy. Soc.* **A157**, 399 (1936).
[74] G. H. Goldschmidt and F. J. Llewellyn, *Acta Cryst.* **3**, 294 (1950).
[75] E. G. Cowley and J. R. Partington, *J. Chem. Soc.* p. 47 (1936).
[76] D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.* p. 2202 (1956).

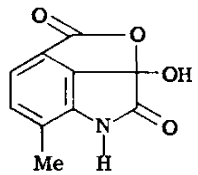
dioxo formulation **73** (R = H). The polarographic behavior of isatin has also been discussed in relation to its tautomerism.[77,78] 7-Methylisatin-4-carboxylic acid has been reported to be in equilibrium with the tricyclic structure **74**.[79]



[72]

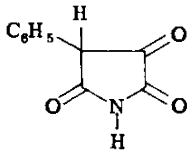


[73]

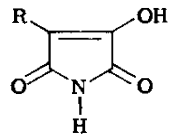


[74]

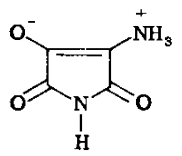
Both the infrared and ultraviolet spectra of pyrrolidine-2,3,5-triones (**75**) have been interpreted to support their existence as hydroxymaleimides (**76**),[80] and the occurrence of a strong OH stretching band in the infrared spectrum of 4-phenylpyrrolidine-2,3,5-trione has been taken as evidence that it too exists in a hydroxy form, probably **76** (R = C_6H_5).[81] However, the trioxo formulation is suggested by the infrared spectra of *N*-substituted pyrrolidine-2,3,5-triones, although an equilibrium apparently occurs depending upon the substituents and conditions.[82] The zwitterion formulation **77** has been advanced for 4-aminopyrrolidine-2,3,5-trione.[83] For chemical evidence



[75]



[76]



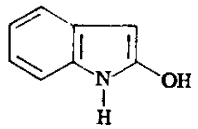
[77]

[77] W. C. Sumpter, J. L. Williams, P. H. Wilkin, and B. L. Willoughby, *J. Org. Chem.* **14**, 713 (1949).
[78] W. C. Sumpter, P. H. Wilkin, J. L. Williams, R. Wedemeyer, F. L. Boyer, and W. W. Hunt, *J. Org. Chem.* **16**, 1777 (1951).
[79] P. W. Sadler, H. Mix, and H. W. Krause, *J. Chem. Soc.* p. 667 (1959).
[80] R. H. Wiley and S. C. Slaymaker, *J. Am. Chem. Soc.* **80**, 1385 (1958).
[81] G. S. Skinner and C. B. Miller, *J. Am. Chem. Soc.* **75**, 977 (1953).
[82] J. C. Sheehan and E. J. Corey, *J. Am. Chem. Soc.* **74**, 360 (1952).
[83] E. G. Howard, A. Kotch, R. V. Lindsey, and R. E. Puttnam, 133rd Meeting, Am. Chem. Soc., Abstr., p. 65N (April 1958, San Francisco).

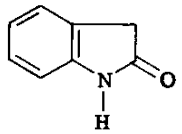
concerning the tautomerism of these compounds, see reference 82 and references therein.

H. Monohydroxyindoles

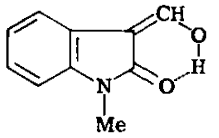
An initial study of the infrared spectrum of oxindole purported to show the presence both of the hydroxy (**78**) and of the oxo forms (**79**),[84] and, indeed, chemical evidence led to the same conclusion.[85] On the basis of later infrared work, however, oxindole and its derivatives were considered to exist more or less completely in the oxo form,[86] and this conclusion is supported by ultraviolet spectroscopic data, i.e., by comparison of the spectrum of the parent compound with those of its methyl derivatives.[87] The infrared spectrum of



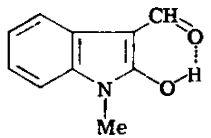
[78]



[79]



[80]



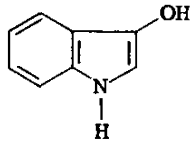
[81]

1-methyloxindole-3-aldehyde is in accord with its formulation as **80** and/or **81**.[65]

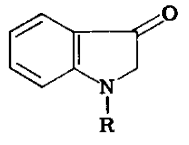
In 1883, the hydroxy structure **82** was assigned to indoxyl on the basis of chemical evidence.[88] More recently, however, the infrared spectra of 1-acetyl- and 1-methyl-indoxyl measured in chloroform indicated that the oxo form **83** (R = Ac, Me) greatly predominates,[40,89]

[84] E. D. Bergmann, *J. Am. Chem. Soc.* **77**, 1549 (1955).
[85] P. L. Julian, J. Pikl, and F. E. Wantz, *J. Am. Chem. Soc.* **57**, 2026 (1935).
[86] A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.* p. 3809 (1956).
[87] Mme. Ramart-Lucas and Mlle. Biquard, *Bull. soc. chim. France* **2**, 1383 (1935).
[88] A. von Baeyer, *Ber. deut. chem. Ges.* **16**, 2188 (1883).
[89] H. C. F. Su and K. C. Tsou, *J. Am. Chem. Soc.* **82**, 1187 (1960).

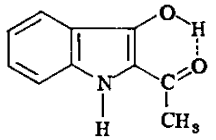
but the presence of an acetyl group in the 2-position has been shown to cause enolization to **84**.[89] The important dyestuff-intermediate, indigo white, is usually formulated as **85** (see, e.g., reference 90), but



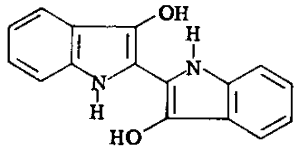
[82]



[83]



[84]

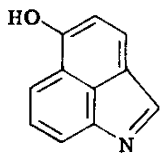


[85]

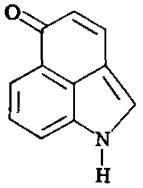
apart from "general phenolic character" there is little definite evidence to support this formulation.

I. Other Compounds with Potential Hydroxyl Groups

Infrared and ultraviolet spectral comparisons by Grob and Hofer[91] show that the position of the equilibrium **86** ⇌ **87** predominantly favors **87**.



[86]

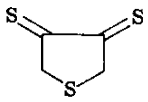


[87]

[90] T. S. Stevens, *in* "Chemistry of the Carbon Compounds" (E. H. Rodd, ed.), Vol. IVB, pp. 1081, 1094. Elsevier, Amsterdam, 1959.
[91] C. A. Grob and B. Hofer, *Helv. Chim. Acta* **36**, 847 (1953).

III. Compounds with Potential Mercapto Groups

Early work on thiophenethiols has been summarized by Hartough,[92] although few conclusions were reached concerning their tautomerism. Caesar and Branton[93] concluded from infrared spectral data that 3-mercaptothiophene existed at least partly in the thiol form but that the 3,4-dithiol existed completely as the dithione **88**. Gronowitz and his associates have recently made a definitive investigation of a series of thiophene-2- and -3-monothiols using nuclear magnetic



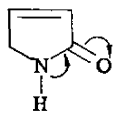
[*88*]

resonance[34,94,95] and infrared spectroscopy.[34,96] Their results show convincingly that all of these compounds exist predominantly in the thiol form, both as the pure liquid and in cyclohexane solution. Mercapto-pyrroles[97] and -indoles[98] have been characterized, but little is known about their tautomerism.

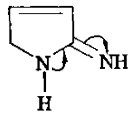
IV. Compounds with Potential Amino Groups

The amino form is usually much more favored in the equilibrium between amino and imino forms than is the hydroxy form in the corresponding keto-enol equilibrium. Grob and Utzinger[99] suggest that in the case of α-amino- and α-hydroxy-pyrroles, structure **89** increases the mesomeric stabilization and thus offsets the loss of pyrrole resonance energy, but the increase due to structure **90** is not sufficient to offset this loss. Similar reasoning may apply to furans and

[92] H. D. Hartough, "Thiophene and Its Derivatives," pp. 428–429. Interscience, New York, 1952.
[93] P. D. Caesar and P. D. Branton, *Ind. Eng. Chem.* **44**, 122 (1952).
[94] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 515 (1961).
[95] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 563 (1961).
[96] S. Gronowitz, P. Moses, and A. B. Hörnfeldt, *Arkiv Kemi* **17**, 237 (1961).
[97] P. Pratesi, *Atti accad. Lincei* **16**, 443 (1932); *Chem. Abstr.* **27**, 2442 (1933).
[98] W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," pp. 53–54. Interscience, New York, 1954.
[99] C. A. Grob and H. Utzinger, *Helv. Chim. Acta* **37**, 1256 (1954).

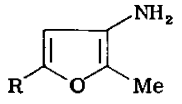


[*89*]

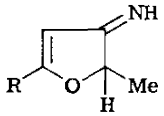


[*90*]

thiophenes. The limited experimental evidence available certainly demonstrates that amino compounds are more stable as such than their hydroxy analogs.



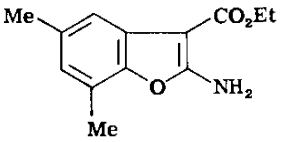
[*91*]



[*92*]

A. Aminofurans

The substituted 3-aminofurans (**91**, R = H, Me) resinify in air, can be diazotized (structure **91**), and are easily hydrolyzed (structure **92** ?).[100] The infrared spectra of both 2- and 3-acetamidofuran show a strong NH stretching band indicating that these compounds do, indeed, exist in the acetamido form.[101]



[*92a*]

The α-aminobenzofuran **92a** exists in the amino form shown, as evidenced by infrared[101a] and proton resonance spectra.[101b]

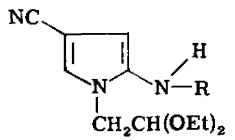
[100] H. B. Stevenson and J. R. Johnson, *J. Am. Chem. Soc.* **59**, 2525 (1937).
[101] R. Kuhn and G. Krüger, *Chem. Ber.* **89**, 1473 (1956).
[101a] J. Derkosch and I. Specht, *Monatsh. Chem.* **92**, 542 (1961).
[101b] A. R. Katritzky and J. Derkosch, *Monatsh. Chem.* **93**, 541 (1962).

B. Aminothiophenes

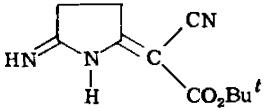
The tautomerism of 2- and 3-aminothiophenes was mentioned by Hartough in his review of thiophenes,[102] but the first definite evidence became available in 1961 when Hoffman and Gronowitz[94] showed conclusively by nuclear magnetic resonance spectroscopy that these compounds both exist in the amino form. In agreement with this finding, 3-aminothiophene generally behaves as an aromatic amine.[103]

C. Aminopyrroles

Aminopyrroles are usually formulated as such because they are quite strong bases and do not easily lose ammonia by hydrolysis.[104,105] In agreement with the amino formulation, the infrared spectrum of the α-aminopyrrole **93** (R = H) contains a νNH_2 doublet and a band near 1660 cm^{-1} corresponding to the NH_2 deformation frequency, and the infrared spectrum of the acetamino derivative is in agreement with the structure **93** (R = Ac).[99] However, a stable imino compound, probably with structure **94**, has been isolated.[56]



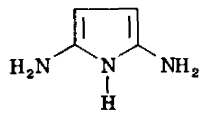
[93]



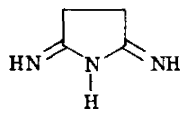
[94]

The relative stability of 2,5-diaminopyrrole- (**95**) and 2,5-diiminopyrrolidine-type (**96**) structures for succimidines has not yet been clarified,[106-108] although ultraviolet spectral data indicate that forms of type **97** are probably unimportant.[109] Banfield[110] has discussed

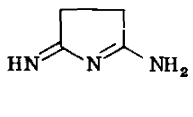
[102] H. D. Hartough, "Thiophene and Its Derivatives," pp. 228–240. Interscience, New York, 1952.
[103] E. Campaigne and P. A. Monroe, *J. Am. Chem. Soc.* **76**, 2447 (1954).
[104] C. A. Grob and P. Ankli, *Helv. Chim. Acta* **33**, 273 (1950).
[105] H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. 1, p. 110 ff. Akademische Verlag., Leipzig, 1934.
[106] G. E. Ficken and R. P. Linstead, *J. Chem. Soc.* p. 3525 (1955).
[107] J. Schurz, A. Ullrich, and H. Bayzer, *Monatsh. Chem.* **90**, 29 (1959).
[108] J. A. Elvidge, *Chem. Soc. (London), Spec. Publ. No. 4*, p. 28 (1956).
[109] J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.* p. 442 (1954).
[110] J. E. Banfield, *J. Chem. Soc.* p. 2098 (1961).



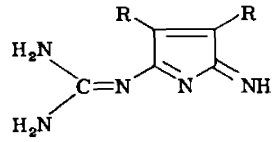
[95]



[96]



[97]

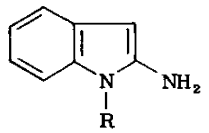


[99]

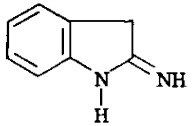
the fine structure of guanidino derivatives of type **99**.

D. Aminoindoles

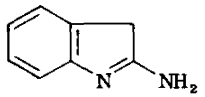
2-Aminoindole was initially assigned structure **100** (R = H) on chemical grounds[111] and later structure **101** was erroneously assigned because the ultraviolet spectrum of its hydrochloride was similar to that of oxindole.[112] In 1956, Kebrle and Hoffmann[113] established the



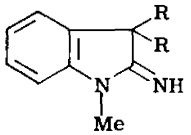
[100]



[101]

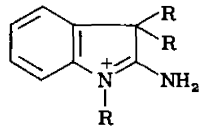


[102]

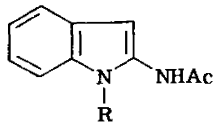


[103]

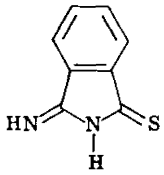
[111] R. Pschorr and G. Hoppe, *Ber. deut. chem. Ges.* **43**, 2543 (1910).
[112] H. Rinderknecht, H. Koechlin, and C. Niemann, *J. Org. Chem.* **18**, 971 (1953).
[113] J. Kebrle and K. Hoffmann, *Helv. Chim. Acta* **39**, 116 (1956).



[104]



[105]



[106]

predominance of structure **102**. 2-Amino-1-methylindole (**100**, R = Me) exists largely in the amino form in ethanol (see later), since its ultraviolet spectrum differs from that of **103** (R = Me). The ultraviolet spectrum of 2-aminoindole differs from both those of **100** (R = Me) and of **103** (R = Me); therefore, it probably exists as **102**. All three bases show similar ultraviolet spectra in acidic solutions indicating that they form similar cations, i.e., of type **104**, and therefore the pK_a method could be used to study these equilibria. Under all conditions, form **102** was found to be the most stable tautomer by a factor >10. The equilibrium between **103** (R = H) and **100** (R = Me) is displaced toward **103** (R = H), the displacement increasing with increasing polarity of the solvent; a comparison of the ultraviolet spectra led to the same conclusion. Infrared spectra support these structural assignments. The acylamino compounds **105** (R = H, Me, Ac)[113] and the isoindole derivative **106**[114] also exist in the forms shown on the basis of infrared and ultraviolet spectral evidence.

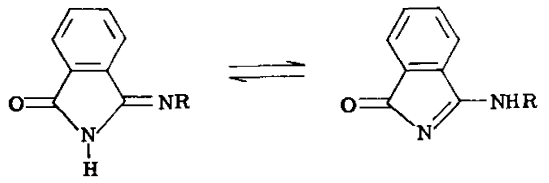
E. Potential Amino Derivatives of Isoindole

Ultraviolet spectral comparisons indicate that structure **107** predominates over **108** when R = H or OH, but that **107** is the predominant form when R = aryl.[115] Similarly, **109** predominates over **110** by a large factor when R = H, OH, or Me, and by a smaller factor when R is a higher alkyl group, but **110** predominates when R is an aryl group. (For a discussion of guanidino derivatives corresponding to **110**, see reference 110.)

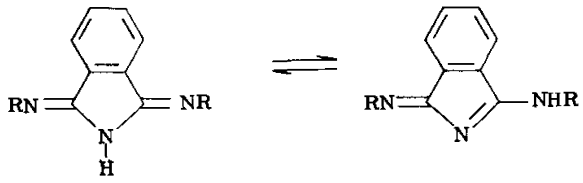
V. Compounds with Potential Methyl Groups

2-Methylene-2,5-dihydrofuran (**111**), which has been isolated by Rice,[116] is converted by acid into 2-methylfuran.

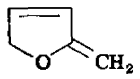
[114] M. E. Baguley and J. A. Elvidge, *J. Chem. Soc.* p. 709 (1957).
[115] P. F. Clark, J. A. Elvidge, and J. H. Golden, *J. Chem. Soc.* p. 4135 (1956).
[116] H. L. Rice, *J. Am. Chem. Soc.* **74**, 3193 (1952).



[107] [108]



[109] [110]

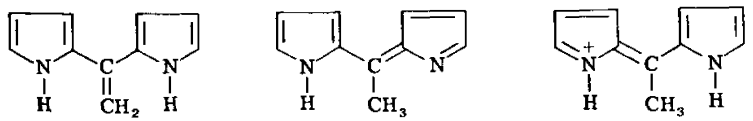


[111]

VI. Other Substituted Pyrroles

A. Vinylpyrroles

The tautomeric equilibrium between **112** and **113** has been studied by Treibs and his associates.[117,118] Most pyrromethenes take form **113** unless both rings carry electron-withdrawing substituents in which case structure **112** is predominant. Common cations of type **114** are favored by both tautomers.

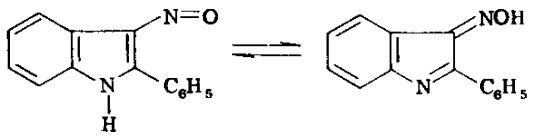


[112] [113] [114]

[117] A. Treibs and F. Reitsam, *Ann. Chem. Liebigs* **611**, 194 (1958).
[118] A. Treibs, E. Herrmann, E. Meissner, and A. Kuhn, *Ann. Chem. Liebigs* **602**, 153 (1957).

B. Nitrosopyrroles

Chemical evidence has been advanced for the formulation of β-nitrosoindoles as either **115** or **116** (see reference 119 and references therein), but ultraviolet spectral comparison with both methylated forms clearly indicated that **116** was favored. Infrared spectral data are also considered to support structure **116**.[120]



[115] [116]

[119] N. Campbell and R. C. Cooper, *J. Chem. Soc.* p. 1208 (1935).
[120] F. Piozzi and M. Dubini, *Gazz. chim. ital.* **89**, 638 (1959).

Prototropic Tautomerism of Heteroaromatic Compounds: IV. Five-Membered Rings with Two or More Hetero Atoms*

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AND
J. M. LAGOWSKI
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* The first two chapters in this volume conclude the series of four articles on prototropic tautomerism; the first two articles appeared in Volume 1. Cross references to these articles include, for easy identification, the roman numeral given in the title.

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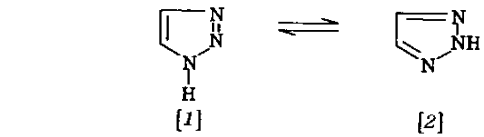
The tautomerism of compounds with five-membered rings and two or more hetero atoms is more complex than that which occurs when only one hetero atom is present. Hydroxy, mercapto, and amino compounds can be in tautomeric equilibrium with oxo, thiocarbonyl, and imino compounds, respectively, in which the proton has moved either to an annular nitrogen atom (as in the six-membered series) or to an annular carbon atom (as in the five-membered rings with one hetero atom; cf. Volume 1, article I, Section I,A). The relative position of a functional group with respect to the hetero atoms often determines the tautomeric nature of these compounds. Therefore, the subject matter in this chapter has been divided into potential hydroxy, mercapto, and amino compounds, and within each of these divisions, compounds with the same relative orientation of functional group and hetero atoms are considered together; e.g., isoxazoles are considered with pyrazoles. If, however, annular $\geqslant$N and =NH groups are present, tautomerism can occur even in the absence of functional groups, and this topic is discussed first for convenience.

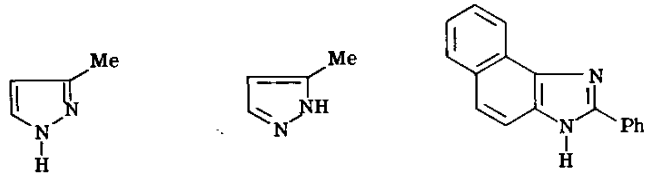
I. Tautomerism Involving Only Annular Nitrogen Atoms

All triazoles, tetrazoles, and unsymmetrically substituted imidazoles and pyrazoles can exist in two tautomeric forms, e.g., **1** $\rightleftharpoons$ **2** and **3** $\rightleftharpoons$ **4**. However, attempts to isolate the individual tautomers have been unsuccessful, always leading to one isomer (for summaries of this aspect of the tautomerism of imidazoles, see references 1 and 2). Although the isolation of both tautomers of a number of com-

[1] H. Green and A. R. Day, *J. Am. Chem. Soc.* **64**, 1167 (1942).
[2] K. Hofmann, "Imidazole and Its Derivatives," pp. 26, 256. Interscience, New York, 1953.



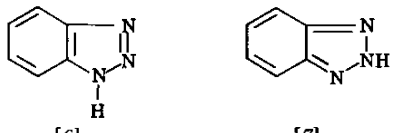
[1] [2]



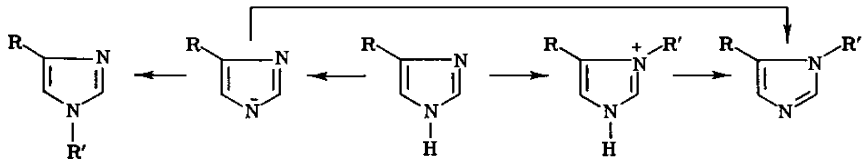
[3] [4] [5]

pounds has been reported, e.g., those of **5**,[3] each report has been disproved[4,5] and no authenticated case is known. Chemical evidence for the rapid interconversion of the individual tautomers of benzotriazoles and benzimidazoles has been summarized by Ingold and Piggott.[6]

In some cases, one tautomeric form might be expected to predominate because of a greater resonance stabilization; for example, the resonance stabilization of **6** should be greater than that of **7** (see following). Chemical evidence has often been adduced for the predominance of one tautomer; however, these data must be interpreted



[6] [7]



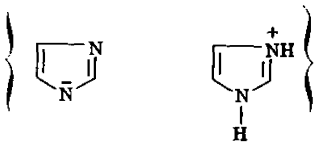
[8] [9] [10] [11] [12]

[3] P. Galimberti, *Gazz. chim. ital.* **63**, 96 (1933).
[4] L. Hunter, *J. Chem. Soc.* p. 806 (1945).
[5] C. F. Kelly and A. R. Day, *J. Am. Chem. Soc.* **67**, 1074 (1945).
[6] C. K. Ingold and H. A. Piggott, *J. Chem. Soc.* **123**, 1469 (1923).

with caution because of the complexity of the systems. For example, alkylation of imidazoles can occur at the nitrogen carrying the hydrogen atom (**10** → **9** → **8**), at the unsubstituted nitrogen (**10** → **11** → **12**), or at both nitrogen atoms (**10** → **9** → **8**, **12**) (see *inter alia* references 7–10).

Pyrazoles and indazoles,[11] imidazoles and benzimidazoles,[12] and benzotriazoles[13] which possess a free NH group are associated and have been considered to exhibit mesohydric tautomerism; see discussion in Volume 1, article I, Section I,C.

It has been suggested that imidazole, 1,3,4-triazole, and tetrazole are ionized in the solid state (cf. **13**).[14] However, a careful assessment of X-ray, dipole moment, and ultraviolet spectral evidence by Zimmerman[15] led to the conclusion that imidazoles are associated but not ionized. The same author has also interpreted the infrared spectra of



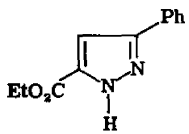
[13]

these compounds in terms of hydrogen-bonded structures and showed that conductivity and basicity considerations preclude a large concentration of ions.[16] The association products of pyrazole have been shown to be cyclic dimers and cyclic trimers by a detailed infrared spectral study.[17]

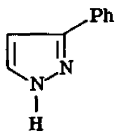
[7] F. Krollpfeiffer, A. Rosenberg, and C. Mühlhausen, *Ann. Chem. Liebigs* **515**, 113 (1935).
[8] O. L. Brady and C. V. Reynolds, *J. Chem. Soc.* p. 2667 (1930).
[9] F. L. Pyman, *J. Chem. Soc.* **121**, 2616 (1922).
[10] K. v. Auwers, *Ber. deut. chem. Ges.* **58**, 2081 (1925).
[11] H. T. Hayes and L. Hunter, *J. Chem. Soc.* p. 1 (1941).
[12] L. Hunter and J. A. Marriott, *J. Chem. Soc.* p. 777 (1941).
[13] T. G. Heafield and L. Hunter, *J. Chem. Soc.* p. 420 (1942).
[14] W. Otting, *Chem. Ber.* **89**, 2887 (1956).
[15] H. Zimmermann, *Z. Elektrochem.* **63**, 601 (1959).
[16] H. Zimmermann, *Z. Elektrochem.* **63**, 608 (1959).
[17] D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, *J. Chem. Soc.* p. 140 (1961).

A. Pyrazoles and Indazoles

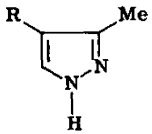
Pyrazoles have received comparatively little attention, but refractivity measurements indicate that **14** and **15** are the predominant forms in their respective equilibria.[18] Wibaut and Boon[19] have reported that structure **16** predominates over **17** (R = H or Me) on the



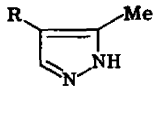
[14]



[15]



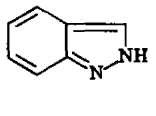
[16]



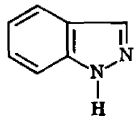
[17]

basis of the products obtained in ozonolysis experiments, but the argument depends on the questionable assumption that ozonolysis proceeds more quickly than tautomeric interconversion.

Early work on the exaltation of the molecular refractivity of indazole and its 1- and 2-alkyl derivatives by Auwers and Düesberg was considered to indicate that structure **18** represented the predomi-



[18]



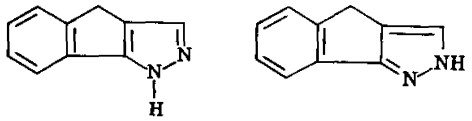
[19]

nant tautomer of the parent compound,[20,21] but further work led Auwers[22] to conclude that structure **19** was the predominant form both for the parent compound and for the C-substituted derivatives studied. A comparison of the ultraviolet spectra of indazole and 1- and 2-methylindazole further supports the predominance of **19**.[23]

The infrared spectrum of the indenopyrazole **20** contains a band at 7.3μ (1381 cm^{-1}) which is considered characteristic of the indene

[18] K. v. Auwers, *Ann. Chem. Liebigs* **508**, 51 (1934).
[19] J. P. Wibaut and J. W. P. Boon, *Helv. Chim. Acta* **44**, 1171 (1961).
[20] K. v. Auwers, *Ann. Chem. Liebigs* **437**, 63 (1924).
[21] K. v. Auwers and M. Düesberg, *Ber. deut. chem. Ges.* **53**, 1179 (1920).
[22] K. v. Auwers, *Ann. Chem. Liebigs* **527**, 291 (1937).
[23] K. Fries, K. Fabel, and H. Eckhardt, *Ann. Chem. Liebigs* **550**, 31 (1942).

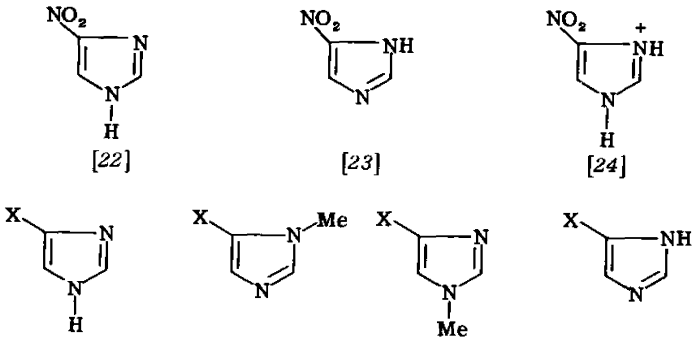
ring and was tentatively interpreted to indicate that the compound does not exist as **21**,[24] but this argument is not compelling.



[20] [21]

B. Imidazoles

Careful examination of 4-nitroimidazole using the basicity method led Grimison, Ridd, and Smith[25] to conclude that structure **22** predominates over **23** by a factor of about 400, and this preference was explained by considering the relative acidities of the two protons in the conjugate acid **24**. The tautomerism of 4-nitroimidazole has been correlated in detail with the relative rates of alkylation at the 1- and 3-positions.[26] These investigators have generalized their experimental findings to a relationship between the predominant tautomeric form of imidazoles and the orientation of the methyl derivatives formed by reaction with dimethyl sulfate.[26] An electron-accepting substituent X in the 4-position should stabilize form **25**; thus methylation of the neutral molecule should give predominantly **26**, whereas methylation



[22] [23] [24]

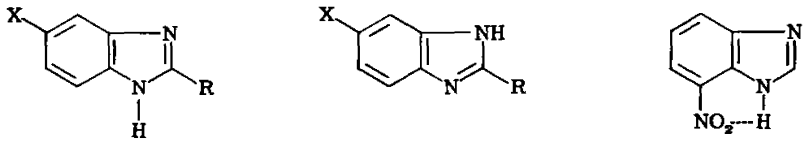
[25] [26] [27] [28]

[24] R. A. Braun and W. A. Mosher, *J. Am. Chem. Soc.* **80**, 4919 (1958).
[25] A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.* p. 1352 (1960).
[26] A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.* p. 1357 (1960).

of the conjugate base should form **26** and **27** with rather more of **27**. If X is an electron-donating substituent, form **28** should be stabilized, and the orientation of the methyl derivatives should be the reverse of the foregoing. Experimental results are in essential agreement with these predictions, which strongly supports the correctness of the structures assigned to the predominant tautomeric forms.[26]

C. Benzimidazoles

By using basicity data, Ridd and Smith[27] showed that 5-nitro- and 5-chloro-benzimidazole and their 2-methyl analogs exist essentially as mixtures of equivalent amounts of **29** and **30**, and, in agreement with this ratio, 5-substituted benzimidazoles form comparable amounts of 1- and 3-derivatives on alkylation,[27] showing earlier alkylation ratios[28,29] to be erroneous. There are, however, other factors which can lead to the predominance of one tautomeric form. Basicity measurements indicate that **31** is preferred to the alternative non-hydro-



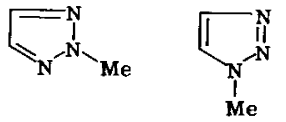
[29] [30] [31]

gen bonded 3*H* form,[27] the presence of intramolecular hydrogen bonding in **31** being supported by the increased volatility and greater ease of reduction of **31** as compared to **29** (R = H, X = NO_2).[29a] The infrared spectra of 5(6)-methyl- and 5(6)-nitro-benzimidazole are of little help in elucidating the fine structure of these compounds.[30] 2-Phenylbenzimidazoles carrying an electron-releasing group in the 5-position are considered to exist in the 1*H* form **29** rather than the 3*H* form since alkylation in mild alkali yields mainly the 3-alkyl derivatives.[31]

[27] J. H. Ridd and B. V. Smith, *J. Chem. Soc.* p. 1363 (1960).
[28] C. E. Hazeldine, F. L. Pyman, and J. Winchester, *J. Chem. Soc.* **125**, 1431 (1924).
[29] M. A. Phillips, *J. Chem. Soc.* p. 1143 (1931).
[29a] J. L. Rabinowitz and E. C. Wagner, *J. Am. Chem. Soc.* **73**, 3030 (1951).
[30] D. G. O'Sullivan, *J. Chem. Soc.* p. 3278 (1960).
[31] N. V. Subba Rao and C. V. Ratnam, *J. Chem. Soc.* p. 3087 (1959).

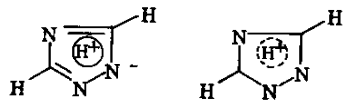
D. Triazoles

Jensen and Friediger[32] found that the dipole moment of 1,2,3-triazole is small and much closer to that of the 2-methyl derivative (**32**) than to that of the 1-methyl derivative (**33**), and they concluded from these data that the symmetrical form (**2**) of the parent compound predominates. Ultraviolet spectral data do not provide unequivocal evidence in this case.[33]



[*32*] [*33*]

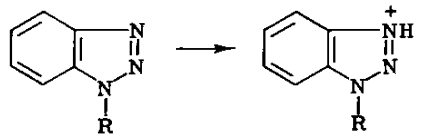
It has recently been suggested[34] that the imino hydrogen atom in 1,2,4-triazoles is not attached to any of the nitrogen atoms but rather that it exists "as a charged atom closely bound by a negatively charged triazole nucleus stabilized by resonance" (e.g., **34** and **35**), but such a representation is considered to be incorrect and misleading by the present authors.



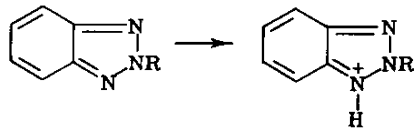
[*34*] [*35*]

E. Benzotriazoles

Comparison of the ultraviolet spectrum of benzotriazole with those of the alkyl derivatives of both forms (cf. **6** and **7**) showed that the 1*H*-form (**6**) was the predominant tautomer[33,35,36]; dipole moment[32] and infrared data[37] support this conclusion. The observation that benzotriazole and 1-alkylbenzotriazoles are much stronger bases than the 2-alkyl derivatives has been used to support the suggestion that the parent compound exists in the 2*H* form (**7**).[36] However, if benzotriazole exists as **6**, as it undoubtedly does, the intrinsic compound **7** must be the stronger base. This apparent contradiction has been resolved by the fact that the 1- and 2-alkyl derivatives do not form a common cation (**36** → **37** and **38** → **39**),[33] the cation **37** apparently being much more stable than **39**.



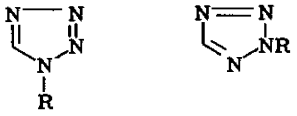
[*36*] [*37*]



[*38*] [*39*]

F. Tetrazoles

The dipole moment of tetrazole is closer to that of the 1-ethyl derivative (**40**, R = Et) than to that of the 2-ethyl derivative (**41**, R = Et) suggesting that the parent compound exists predominantly as **40** (R = H).[38] This conclusion has been confirmed by comparison of



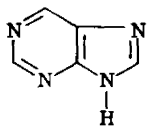
[*40*] [*41*]

the shifts of the —CH proton lines in the nuclear magnetic resonance spectra of various 1- and 2-substituted tetrazoles.[39]

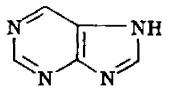
[32] K. A. Jensen and A. Friediger, *Kgl. Danske Videnskab. Selskab, Mat.-fys. Medd.* **20**(20), 1 (1943); *Chem. Abstr.* **39**, 2068 (1945).
[33] Dal Monte Casoni, D. A. Mangini, R. Passerini, and C. Zauli, *Gazz. chim. ital.* **88**, 977 (1958).
[34] K. T. Potts, *Chem. Revs.* **61**, 87 (1961).
[35] H. Specker and H. Gawrosch, *Ber. deut. chem. Ges.* **75**, 1338 (1942).
[36] F. Krollpfeiffer, H. Pötz, and A. Rosenberg, *Ber. deut. chem. Ges.* **71**, 596 (1938).
[37] D. G. O'Sullivan, *J. Chem. Soc.* p. 3653 (1960).
[38] M. H. Kaufman, F. M. Ernsberger, and W. S. McEwan, *J. Am. Chem. Soc.* **78**, 4197 (1956).
[39] D. W. Moore and A. G. Whittaker, *J. Am. Chem. Soc.* **82**, 5007 (1960).

G. Purines

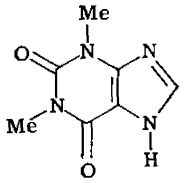
Molecular orbital theory indicates that there is little difference between the stability of the two tautomers of purine, **42** and **43**.[40] Molecular orbital calculations indicate that purine forms a monocation by protonation at N-3[41] or at N-1.[42] A precise X-ray crystallographic study indicates that theophylline exists in the "*7H*" form **44**.[43]



[*42*]



[*43*]

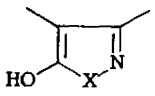


[*44*]

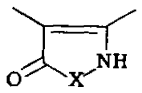
II. Compounds with Potential Hydroxyl Groups

A. Hetero Atoms-1,2 and a Potential 3-(or 5-)Hydroxyl Group

A great deal of work has appeared on these compounds; however, much of it was mutually contradictory and a clear pattern is only now appearing for the tautomerism of compounds of this type. Compounds with potential 5-hydroxyl groups, which could exist as **44a**, **44b**, or **44c** (X = O or NR), never appear in the hydroxy form (unless this is stabilized by chelation): the two oxo forms, **44b** and **44c**, exist in equilibrium. However, compounds with potential 3-hydroxyl groups *do* exist as such, i.e., as **44d** and not as **44e**. This

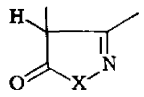


[*44a*]

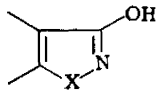


[*44b*]

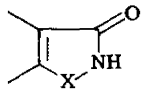
[40] A. Pullman and B. Pullman, *Bull. soc. chim. France* p. 766 (1958).
[41] S. F. Mason, *in* "Ciba Foundation Symposium on the Chemistry and Biology of Purines" (G. E. W. Wolstenholme and C. M. O'Connor, eds.), p. 72. Little, Brown, Boston, Massachusetts, 1957.
[42] T. Nakajima and B. Pullman, *Bull. soc. chim. France* p. 1502 (1958).
[43] D. J. Sutor, *Acta Cryst.* **11**, 83 (1958).



[*44c*]



[*44d*]

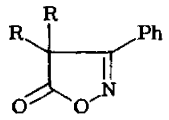


[*44e*]

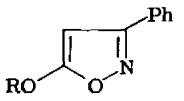
existence in the OH form is possibly associated with the spare pair of electrons on the atom adjacent to the nitrogen atom.

1. *Isoxazol-5-ones*

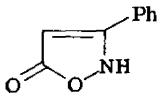
Isoxazol-5-ones can exist in three different types of structures, cf. **45**–**47** (R = H). Early investigators assigned structures to these compounds on the basis of unreliable chemical evidence; thus the NH structure **47** was favored because the silver salt of 3-phenylisoxazol-5-one reacts with methyl iodide to give a product which was incorrectly (see reference 44) formulated as the *N*-methyl derivative[45] (cf. also reference 46). Bromine titration data led to assignment of an incorrect structure to 3,4-diphenylisoxazol-5-one; cf. article I (Volume 1), Section II,A. Comparison of the dipole moments of 3-phenylisoxazol-5-one with those of the methyl derivatives **45** (R = Me) and **46**



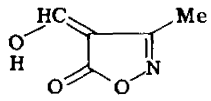
[*45*]



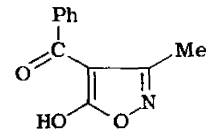
[*46*]



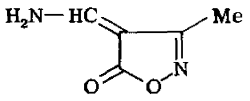
[*47*]



[*48*]



[*49*]



[*50*]

(R = Me) and especially infrared spectral data indicated that 3-phenylisoxazol-5-one exists in the CH form (**45**, R = H).[47] The

[44] P. Grünanger and M. R. Langella, *Gazz. chim. ital.* **89**, 1784 (1959).
[45] R. Uhlenhuth, *Ann. Chem. Liebigs* **296**, 33 (1897).
[46] E. Oliveri-Mandala and A. Coppola, *Atti reale accad. Lincei, Rend classe sci. fis. mat. e nat.* **20**, I, 244 (1911); *Chem. Abstr.* **5**, 2100 (1911).
[47] C. L. Angyal and R. J. W. LeFèvre, *J. Chem. Soc.* p. 2181 (1953).

infrared spectra of 4-formylisoxazol-5-ones indicate that they exist in the 4-hydroxymethylene form **48**, but the infrared spectra of the benzoyl analogs are in accord with the hydroxy-isoxazole structure **49**.[48] However, German workers[48a] have argued that these benzoyl (and analogous) derivatives also exist with the hydroxyl group on the exocyclic carbon atom: such compounds are, of course, chelated and this diminishes the difference between these two formulations. The nitrogen analogs of **48** exist as **50**.[48]

Recently a definitive study of several isoxazol-5-ones using infrared and ultraviolet spectroscopy (Table I) has shown that the balance between the various tautomers is a delicate one and that all three of the structural types can predominate depending upon the nature of the substituents and the conditions of the experiment.[49,50] However, the hydroxy form is only found when it is stabilized by chelation (i.e., a carbonyl substituent in the 4-position). The other compounds exist in the CH form in nonpolar media: increasing polarity of the solvent stabilizes increasing amounts of the more polar NH forms.

2. *Isoxazol-3-ones*

Italian investigators have recently shown by infrared spectroscopy that 3-hydroxy-5-phenylisoxazole exists as such and *not* in the isoxazolone form.[51] This conclusion is supported by a spectroscopic investigation of the 4,5-dimethyl and other dialkyl analogs.[51a]

3. *Saccharin*

Structure **51** has been assigned to saccharin on the basis of infrared spectral data.[30]

4. *1-Substituted Pyrazol-5-ones*

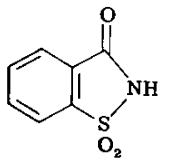
These compounds can exist in the three tautomeric forms illustrated by structures **52–54**, which will be referred to as the OH, CH, and

[48] S. V. Sokolov and I. Ya. Postovskiĭ, *Zhur. Obshcheĭ Khim.* **30**, 600 (1960); *Chem. Abstr.* **54**, 24658 (1960).
[48a] F. Korte and K. Störiko, *Chem. Ber.* **94**, 1956 (1961).
[49] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).
[50] A. R. Katritzky and S. Øksne, *Tetrahedron* **18**, 777 (1962).
[51] P. Bravo, G. Gaudiano, A. Quilico, and A. Ricca, *Gazz. chim. ital.* **91**, 47 (1961).
[51a] A. R. Katritzky, S. Øksne, and A. J. Boulton, unpublished work (1961–62).

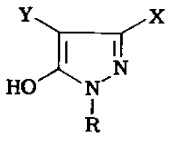
TABLE I
TAUTOMERIC COMPOSITION OF ISOXAZOL-5-ONES (%)[a]

Substituents 3-	4-	UV C_6H_{12}	NMR[b]	IR C_2Cl_4	IR $CHCl_3$	UV H_2O	IR Nujol
Me	H	CH	CCl_4: CH	—	CH	70CH + 30NH	CH
t-Bu	H	CH	CCl_4: CH	—	CH	70CH + 30NH	CH
C_6H_5	H	CH	$CHCl_3$: CH	—	CH	70CH + 30NH	CH
p-NO_2-C_6H_4	H	CH	—	—	CH	80CH + 20NH	CH
p-MeO-C_6H_4	H	CH	—	—	CH	80CH + 20NH	CH
—$(CH_2)_4$—		95CH + 5NH	$CHCl_3$: CH with some NH	—	80CH + 20NH	NH	NH
C_6H_5	Me	CH	$CHCl_3$: 40CH + 60NH	90CH + 10NH	40CH + 60NH to 75CH + 25NH	NH	NH
t-Bu	Br	CH	—	—	95CH + 5NH	NH	NH
C_6H_5	Br	CH	—	CH	90CH + 10NH	20CH + 80NH	NH
p-NO_2-C_6H_4	Br	?	—	—	CH	?	NH
p-MeO-C_6H_4	Br	?	—	—	CH	?	NH
Me	CO_2Et	OH	Me_2CO: OH + some NH	—	OH + NH	NH	NH
C_6H_5	CO_2Et	OH	$CHCl_3$ } OH + some NH Me_2CO }	—	OH + NH	NH	NH

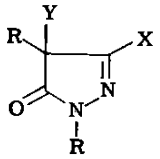
[a] Taken from A. R. Katritzky and S. Øksne, *Tetrahedron* **18**, 777 (1962).
[b] Solvent given.



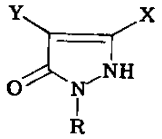
[51]



[52]



[53]



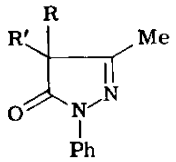
[54]

NH forms, respectively. Although considerable work has been reported on these compounds, much of it was, or appeared to be, contradictory, and only recently has the complex pattern of the tautomerism which occurs in this series become clear.[52]

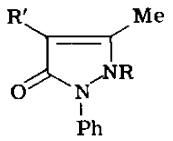
As early as 1895, Knorr realized that three types of derivatives could be formed for this type of compound, corresponding to the three tautomeric structures.[53] Other early investigators assigned an oxo structure to these compounds on the basis of tenuous chemical evidence,[54] while still others discussed the tautomerism without reaching any definite conclusions.[55,56]

Biquard and Grammaticakis[57] demonstrated in 1941 that the ultraviolet spectra of 3-methyl- and 3,4-dimethyl-1-phenylpyrazol-5-one were intermediate between those of methylated derivatives of the CH (i.e., **55**, R = R′ = Me) and NH forms (i.e., **56**, R = Me, R′ = H or Me) of the compounds, concluding that the potentially tautomeric compounds exist as mixtures of these forms. However, they did not consider the possible occurrence of an OH form. Other ultraviolet

[52] A. R. Katritzky and F. Maine, *Tetrahedron*, in press.
[53] L. Knorr, *Ber. deut. chem. Ges.* **28**, 706 (1895).
[54] A. Michaelis and F. Engelhardt, *Ber. deut. chem. Ges.* **41**, 2668 (1908).
[55] H. Beyer and D. Stehwien, *Arch. Pharm.* **286**, 13 (1953).
[56] W. Krohs, *Chem. Ber.* **88**, 866 (1955).
[57] D. Biquard and P. Grammaticakis, *Bull. soc. chim. France* **8**, 246 (1941).



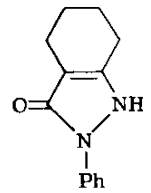
[55]



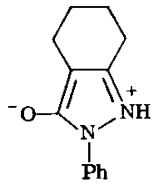
[56]

spectral studies reported about this time were even less conclusive.[58-60] In 1953, an oxo structure was assigned to 4-monosubstituted 1,3-diphenylpyrazol-5-ones on the basis of ultraviolet and infrared spectral data.[61]

The infrared spectra of the crystalline compounds have been reported by several investigators. Carpino[62] found that 4,4-disubstituted pyrazol-5-ones exibit an absorption band in the 5.63-5.84μ (1780-1710 cm^{-1}) region of the spectrum but that both the unsubstituted compounds and the compounds monosubstituted in the 4-position did not show this absorption band, which led him to conclude that the latter two types of compounds must exist in the NH or OH form. In 1959, American investigators[63] reached similar conclusions for the 1-phenyl-3,4-tetramethylene and 1,3-dimethyl derivations and assigned the strong absorption at ca. 2600 cm^{-1} to zwitterion $\geqslant\overset{+}{N}$—H



[57]



[58]

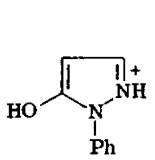
[58] N. A. Valyashko and V. I. Bliznyukov, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **11**, 559 (1941); *Chem. Abstr.* **35**, 7961 (1941).
[59] N. A. Valyashko and V. I. Bliznyukov, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **10**, 1343 (1940); *Chem. Abstr.* **35**, 3633 (1941).
[60] N. A. Valyashko and V. I. Bliznyukov, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **11**, 23 (1941); *Chem. Abstr.* **35**, 5496 (1941).
[61] P. E. Gagnon, J. L. Boivin, and R. J. Paquin, *Can. J. Chem.* **31**, 1025 (1935).
[62] L. A. Carpino, *J. Am. Chem. Soc.* **80**, 5796 (1958).
[63] G. deStevens, A. Halamandaris, P. Wenk, and L. Dorfman, *J. Am. Chem. Soc.* **81**, 6292 (1959).

and NH structures of the type **57** which were considered to include large contributions from canonical forms such as **58**. The infrared spectra of several pyrazolones have been interpreted on the basis of the Δ^2-5-one formulation by a German group,[64] but this formulation has been questioned.[62,65] Refn[66] concluded from infrared spectral studies that a series of 1,3-disubstituted pyrazol-5-ones exist in the OH form **52** (R, X = Me or aryl) in the crystalline state, and it was further concluded from pK_a data that approximately equal amounts of the NH and OH forms exist in aqueous (?) solution (see following). Other investigators have discussed the acidity and basicity of pyrazolone with reference to its tautomeric forms.[67-69]

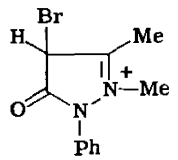
Janssen and Ruysschaert[65] found that 1-phenyl-3-methylpyrazol-5-one showed infrared absorption bands at **1705** and **1625** cm^{-1} in chloroform solution, demonstrating its existence at least partly in the CH form; in addition to these bands, another band occurred at 3610 cm^{-1} in acetonitrile, leading to the suggestion that a mixture of CH and OH forms exists in the latter solvent. The spectrum of the solid compound was considered to be in accord with either the NH or OH form, strongly hydrogen bonded.[65] A German group[70] also studied the infrared spectra of this compound and its 4-methyl derivative and concluded that the compounds exist in the CH form in chloroform solution and in the OH form in the solid state. 1-(2,4-Dinitrophenyl)-3-phenylpyrazol-5-one has been shown to exist in the CH form in chloroform solution using infrared and nuclear magnetic resonance spectroscopy.[71]

The ultraviolet spectra of 1-phenylpyrazol-5-ones, particularly the bromo derivatives, were studied by Westöö.[72] He concluded that the monocations were usually of structure **59**, but that the monocation from bromoantipyrine was in equilibrium with **60** under some circumstances. The spectrum of 4-bromo-3-methyl-1-phenylpyrazol-5-one corresponds to that of its 4-methyl derivative in chloroform, suggesting that it exists as **61** in this solvent, but the spectrum in ethanol is greatly changed, indicating that another form predominates in the latter solvent.

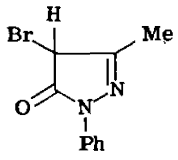
[64] R. Hüttel, E. Wagner, and B. Sickenberger, *Ann. Chem. Liebigs* **607**, 109 (1957).
[65] R. Janssen and H. Ruysschaert, *Bull. soc. chim. Belges* **67**, 270 (1958).
[66] S. Refn, *Spectrochim. Acta* **17**, 40 (1961).
[67] S. Veibel, K. Eggersen, and S. C. Linholt, *Acta Chem. Scand.* **8**, 768 (1954).
[68] S. Veibel, J. Kjaer, and E. Plejl, *Acta Chem. Scand.* **5**, 1283 (1951).
[69] S. Veibel, K. Eggersen, and S. C. Linholt, *Acta Chem. Scand.* **6**, 1066 (1952).
[70] W. Pelz, W. Püschel, H. Schellenberger, and K. Löffler, *Angew. Chem.* **72**, 967 (1960).
[71] R. M. Silverstein and J. N. Shoolery, *J. Org. Chem.* **25**, 1355 (1960).
[72] G. Westöö, *Acta Chem. Scand.* **6**, 1499 (1952).



[59]

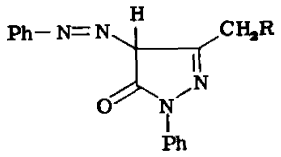


[60]

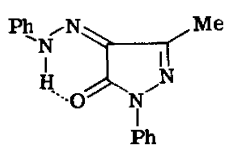


[61]

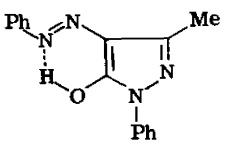
The infrared spectra of 4-arylazopyrazol-5-ones have been successively interpreted to support structures **62** (R = *o*-ClC_6H_4),[73] either **62** (R = Me) or **63**,[74] **63**,[75] and **64**.[70] The available ultraviolet spectral evidence favors structure **64**.[70]



[62]

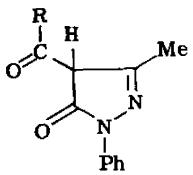


[63]

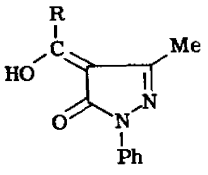


[64]

4-Acylpyrazol-5-ones can often be obtained in two crystalline forms which have been considered to be the keto (**65**) and enol (**66**) modifications of the acyl group.[54,76]



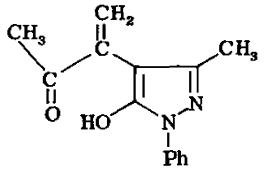
[65]



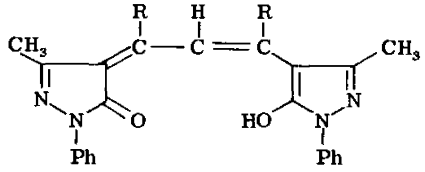
[66]

[73] H. Dahn and G. Rotzler, *Helv. Chim. Acta* **43**, 1555 (footnote p. 1557) (1960).
[74] F. A. Snavely and F. H. Suydam, *J. Org. Chem.* **24**, 2039 (1959).
[75] S. Toda, *Nippon Kagaku Zasshi* **80**, 402 (1959); *Chem. Abstr.* **55**, 4150 (1961).
[76] B. S. Jensen, *Acta Chem. Scand.* **13**, 1668 (1959).

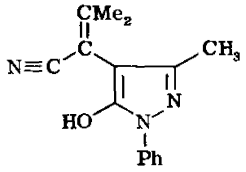
Westöö[77] has proposed that **67** has the structure shown on the basis of its infrared spectrum (ν C=O at 1670 cm^{-1} and ν OH ca. 2500 cm^{-1}) and other evidence, and he has also discussed the tautomerism of compounds of type **68**[77] and **69**.[78]



[67]



[68]



[69]

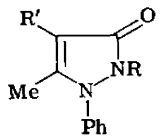
5. *1-Substituted Pyrazol-3-ones*

The ultraviolet spectra of compounds which may exist as either 1-substituted pyrazol-3-ones (**70**, R = H) or 1-substituted 3-hydroxypyrazoles (**71**, R = H) do not allow distinction between the two possible forms, because their spectra and those of fixed derivatives of both types (**70**, R = Me and **71**, R = Me) are too similar.[79] The solid state infrared spectra of these compounds have been interpreted to support both the NH form[63] (see reference 79a for a similar conclusion regarding indazol-3-one) and the OH form.[66] Basicity data have also been considered to indicate the predominance of the OH form.[66]

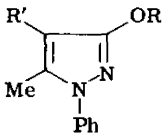
6. *Other Pyrazol-3- and -5-ones*

If the nitrogen atoms of this type of compound do not carry a substituent, two mobile hydrogen atoms and eight tautomeric forms (**72**–

[77] G. Westöö, *Acta Chem. Scand.* **13**, 679 (1959).
[78] G. Westöö, *Acta Chem. Scand.* **13**, 683 (1959).
[79] D. Biquard and P. Grammaticakis, *Bull. soc. chim. France* **8**, 254 (1941).
[79a] D. G. O'Sullivan, *J. Chem. Soc.* p. 3278 (1960).

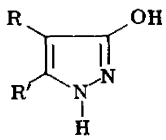


[70]

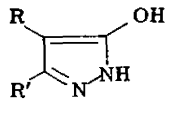


[71]

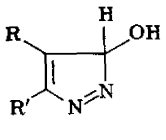
79) are possible, hence it is not too surprising that the conclusions which have been drawn regarding the structures of these compounds



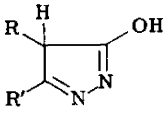
[72]



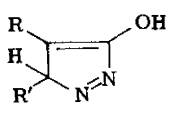
[73]



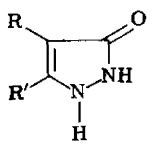
[74]



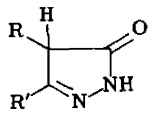
[75]



[76]



[77]



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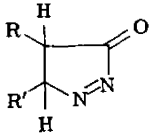


[79]

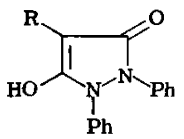
are very speculative. In 1895, 3-phenylpyrazol-5-one was reported to yield a methoxy derivative on reaction with diazomethane, and this observation was considered to indicate that a hydroxy form predominates.[80] The infrared spectra of several crystalline compounds of this type have been discussed,[62,63,66] but no definite conclusions were reached concerning the relative abundance of the various tautomers.

[80] H. v. Pechmann, *Ber. deut. chem. Ges.* **28**, 1624 (1895).

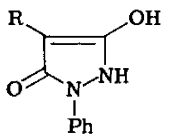
Infrared spectral evidence indicates that indazol-3-one probably exists in the oxo form (cf. **77**).[80] 4-Monosubstituted-1,3-diphenylpyrazol-5-ones have been assigned an oxo structure (cf. **78**) on the basis of infrared (presence of a ν C=N band) and ultraviolet spectral data.[61] The structure of certain *N*-acylated pyrazolones has been discussed on the basis of their infrared spectra,[81] but in these cases the possibility of acyl migration is a complicating factor.

7. *Pyrazol-3,5-diones*

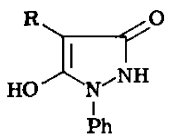
1,2-Diphenylpyrazol-3,5-diones give a positive enol test with ferric chloride and form methoxy compounds with diazomethane, and on the basis of this evidence they were originally formulated as monohydroxy compounds (**80**).[82] The 1-phenyl analogs have also been formulated as monohydroxy compounds **81** or **82**, although their ultra-



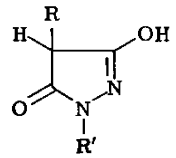
[*80*]



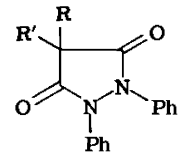
[*81*]



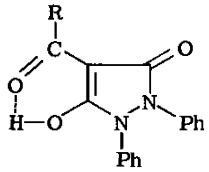
[*82*]



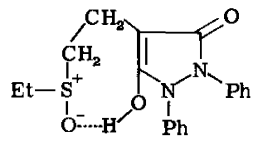
[*83*]



[*84*]



[*85*]



[*86*]

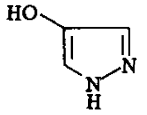
[81] E. Wahlberg, *Arkiv Kemi* **17**, 83 (1961).
[82] H. Ruhkopf, *Ber. deut. chem. Ges.* **73**, 820 (1940).

violet spectra are similar to those of the 4,4-disubstituted derivatives.[83] Structures of types **81**, **82**, and **83** have been suggested for the analogous 1-chlorophenyl compounds since the infrared spectra show bands corresponding to an enolic —C=C—OH group and a —C=N— group.[84] It has now become clear, however, that most compounds of this class exist in the dioxo form **84**. The infrared spectra show two ν C=O bands at ca. 5.7 and 5.8μ (1775 and 1725 cm^{-1}), and the presence of one or two substituents at the 4-position has little effect on the infrared[85-88] or ultraviolet spectra[88] of these compounds. Substituents which can form intramolecular hydrogen bonds with a hydroxyl group stabilize the enolic form, e.g., structures **85**[85] and **86**[88] are stable.

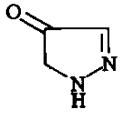
In the 1,2-diphenyl-4-alkoxy series, the keto and enol forms have both been isolated: the latter is unstable and changes irreversibly into the former.[88a]

B. Hetero Atoms-1,2 and a Potential 4-Hydroxyl Group

4-Hydroxypyrazoles have been tentatively concluded to exist as equilibrium mixtures containing both the hydroxy (cf. **87**) and the oxo forms (cf. **88**) since they give a positive enol test with ferric chloride



[*87*]



[*88*]

and form *O*-benzoyl derivatives.[88b] 4-Hydroxy-3,5-diphenylisoxazole has been tentatively assigned a 4-hydroxy structure on the basis of chemical evidence.[89]

[83] P. E. Gagnon, J. L. Boivin, and P. A. Brown, *Can. J. Research* **28B**, 720 (1950).
[84] P. E. Gagnon, J. L. Boivin, R. MacDonald, and L. Yaffe, *Can. J. Chem.* **32**, 823 (1954).
[85] W. Logemann, F. Lauria, and V. Zamboni, *Chem. Ber.* **88**, 1353 (1955).
[86] W. Logemann, F. Lauria, and V. Zamboni, *Chem. Ber.* **89**, 620 (1956).
[87] C. Cardani, A. Mantegani, B. Cavalleri, and I. L. Sianesi, *Gazz. chim. ital.* **90**, 1746 (1960).
[88] E. Girod, R. Delley, and F. Häfliger, *Helv. Chim. Acta* **40**, 408 (1957).
[88a] K. M. Hammond, N. Fisher, E. N. Morgan, E. M. Tanner, and C. S. Franklin, *J. Chem. Soc.* p. 1062 (1957).
[88b] F. D. Chattaway and H. Irving, *J. Chem. Soc.* p. 786 (1931).
[89] A. H. Blatt and W. L. Hawkins, *J. Am. Chem. Soc.* **56**, 2190 (1934).

C. Hetero Atoms-1,3 and a Potential 2-Hydroxyl Group

All the available evidence suggests that five-membered heterocyclic compounds containing a potential hydroxyl group between the two hetero atoms in the 1- and 3-positions exist predominantly in the oxo form (cf. **89**⇌**90**).

[*89*] [*90*]

1. *Oxazol-2-ones*

The similarity of the ultraviolet spectrum of 4,5-diphenyloxazol-2-one (**91**) with those of both alternative methyl derivatives preclude application of the spectral comparison method to the elucidation of their structures, but the fluorescence spectra of these compounds indicate that **91** exists in the oxo form.[90] Infrared data for a number of substituted oxazol-2-ones support this conclusion.[91]

In 1900, ultraviolet data were used to show that benzoxazol-2-one

[*91*] [*92*]

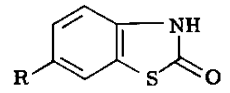
(**92**) exists as such,[92] and this structural assignment was later confirmed by infrared spectroscopy.[30,93] The fact that benzoxazol-2-one[94] and its 4-, 5-, 6-, and 7-mononitro[95] and 5,7-dinitro derivatives[96] give

[90] R. Gompper and H. Herlinger, *Chem. Ber.* **89**, 2816 (1956).
[91] R. Gompper and H. Herlinger, *Chem. Ber.* **89**, 2825 (1956).
[92] W. N. Hartley, J. J. Dobbie, and P. G. Paliatseas, *J. Chem. Soc.* **77**, 839 (1900).
[93] E. E. Smissman, J. B. LaPidus, and S. D. Beck, *J. Am. Chem. Soc.* **79**, 4697 (1957).
[94] H. Zinner and H. Herbig, *Chem. Ber.* **88**, 693 (1955).
[95] H. Zinner, H. Herbig, I. Wistup, and H. Wigert, *Chem. Ber.* **92**, 407 (1959).
[96] H. Zinner and H. Herbig, *Chem. Ber.* **88**, 1241 (1955).

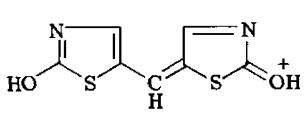
N-substitution products (e.g., with diazomethane) was advanced by Zinner and his coworkers in support of the NH formulation for these compounds; however, these authors have recently directed attention to the inconclusive nature of such evidence.[97]

2. *Thiazol-2-ones*

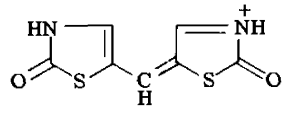
Early attempts to study the structure of thiazol-2-one by comparison of its ultraviolet spectrum with those of both alkylated forms failed because of the similarity of the spectra in the region investigated.[98] However, in 1935, this method was successfully applied to benzothiazol-2-one (**93**)[99] and in 1954 to thiazol-2-one itself,[100,100a] indi-



[*93*]



[*94*]



[*95*]

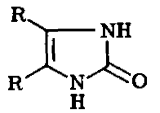
cating the predominance of the oxo forms for both compounds. Infrared spectral data (ν NH, ν C=O) also suggest that thiazol-2-one[100,101] and some of its substituted derivatives[102,100a] exist primarily in the oxo form. The related compound, benzoselenazol-2-one, has been shown to exist as such using ultraviolet spectroscopy.[103] Structure

[97] H. Zinner and H. Wigert, *Chem. Ber.* **93**, 1331 (1960).
[98] A. Hantzsch, *Ber. deut. chem. Ges.* **60**, 2537 (1927).
[99] R. F. Hunter and E. R. Parken, *J. Chem. Soc.* p. 1755 (1935).
[100] G. Klein and B. Prijs, *Helv. Chim. Acta* **37**, 2057 (1954).
[100a] Yu. N. Sheĭnker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* **33**, 2096 (1959) [English translation: *Russian J. Phys. Chem.* **33**, 303 (1959)].
[101] M. G. Ettlinger, *J. Am. Chem. Soc.* **72**, 4699 (1950).
[102] G. deStevens, A. Frutchey, A. Halamandaris, and H. A. Luts, *J. Am. Chem. Soc.* **79**, 5263 (1957).
[103] R. D. Desai, R. F. Hunter, and A. R. K. Khalidi, *J. Chem. Soc.* p. 321 (1938).

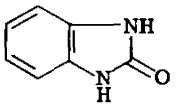
94 was preferred to **95**, but the argument presented (based on aromaticity)[104] is not at all compelling.

3. *Imidazol-2-ones*

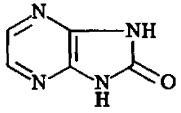
Infrared spectral data[91] have been advanced to support the oxo formulation for **96** (R = propyl). Structure **96** (R = phenyl) has also been proposed on the basis of the fact that benzoin does not condense with urea,[105] and this conclusion is probably correct, although the argument is not convincing. The oxo forms of benzimidazolone, **97**,[106,107] and the related pyrazinoimidazolone **98**[107] have been shown to predominate using infrared spectroscopy. Ultraviolet spectral comparisons indicate that **99** exists largely in the oxo form.[108] The only



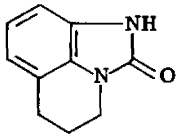
[96]



[97]



[98]



[99]

evidence that 2-oxoimidazoles exist in an appreciable proportion of the hydroxy form is the positive ferric chloride reaction observed in solution.[109]

D. Hetero Atoms-1,3 and a Potential 4-(or 5)Hydroxyl Group

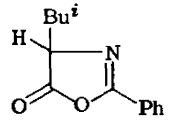
Available evidence shows that these compounds exist in the oxo form except when an electron-withdrawing group is present in the 5-(or 4-)position.

1. *Oxazol-5-ones*

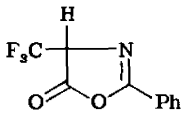
The fact that oxazol-5-ones such as **100** can be obtained optically active indicates that they must exist in the CH form, e.g., as **100**.[110]

[104] E. B. Knott, *J. Chem. Soc.* p. 4244 (1960).
[105] R. Roger, K. C. Reid, and R. Wood, *J. Chem. Soc.* p. 3453 (1954).
[106] D. Harrison and A. C. B. Smith, *J. Chem. Soc.* p. 3157 (1959).
[107] S. F. Mason, *J. Chem. Soc.* p. 4874 (1957).
[108] A. Richardson and E. D. Amstutz, *J. Org. Chem.* **25**, 1138 (1960).
[109] K. Hofmann, "Imidazole and Its Derivatives," p. 62. Interscience, New York, 1953.
[110] J. W. Cornforth, *in* "The Chemistry of Penicillin" (H. T. Clarke, J. R. Johnson, and R. Robinson, eds.), p. 742. Princeton Univ. Press, Princeton, New Jersey, 1949.

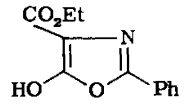
This formulation is supported by the proton resonance spectrum of the trifluoromethyl compound **101** which shows that it exists in the CH form shown.[111] However, strong electron-withdrawing groups in the 4-position apparently lead to enolization, and compound **102**, for example, gives an intense color with ferric chloride.[112] Other 4-acylated oxazol-5-ones are often formulated as **103** (see, e.g., reference 113). Tautomerism of the type illustrated by the equilibrium **104** ⇌ **105** has been discussed[114] (see reference 115 for further references).



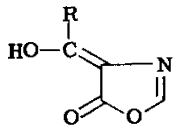
[100]



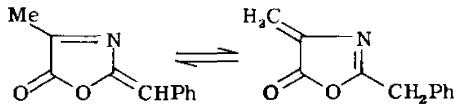
[101]



[102]



[103]



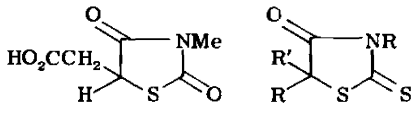
[104] [105]

2. *Thiazol-4- and -5-ones*

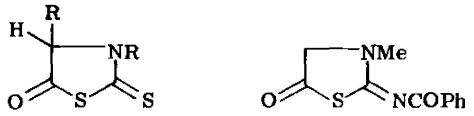
The thiazole-2,4-dione **105a** has been obtained optically active,[116] demonstrating the existence of the dioxo form. Rhodanines are usually written in the carbonyl form (**106**, R, R′ = H or alkyl) (cf. reference **117**), and this formulation is supported by infrared,[118] ultraviolet,[118]

[111] F. Weygand and W. Steglich, *Angew. Chem.* **73**, 433 (1961).
[112] J. W. Cornforth, *in* "The Chemistry of Penicillin" (H. T. Clarke, J. R. Johnson, and R. Robinson, eds.), pp. 775, 787. Princeton Univ. Press, Princeton, New Jersey, 1949.
[113] E. J. Bourne, J. Burdon, V. C. R. McLoughlin, and J. C. Tatlow, *J. Chem. Soc.* p. 1771 (1961).
[114] J. A. King and F. H. McMillan, *J. Am. Chem. Soc.* **72**, 833 (1950).
[115] J. W. Cornforth, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. V, pp. 373–375. Wiley, New York, 1957.
[116] S. Kallenberg, *Ber. deut. chem. Ges.* **56**, 316 (1923); cf. F. C. Brown, *Chem. Revs.* **61**, 463 (1961).
[117] A. Mustafa, W. Asker, S. Khattab, M. E. E. D. Sobhy, A. M. Fleifel, and K. Abu-Elazayem, *J. Am. Chem. Soc.* **82**, 2029 (1960).
[118] F. C. Brown, C. K. Bradsher, B. F. Moser, and S. Forrester, *J. Org. Chem.* **24**, 1056 (1959).

and X-ray crystallographic evidence.[119] The isomeric thiazol-5-one derivatives of type **107** have been shown to exist in the oxo-thione form using infrared spectroscopy[120]; similarly, X-ray work[120a] demonstrates the existence of the oxo form for **107a.**



[*105a*] [*106*]



[*107*] [*107a*]

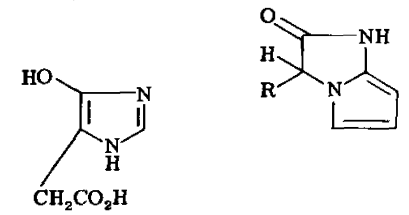
3. *Imidazol-4-ones*

Optically active imidazol-4-one-5-acetic acid has been prepared by Kny and Witkop,[121] and therefore it must exist as **108** or **109** rather than as **110.** Similarly, Grob and Ankli[122] have presented ultraviolet and infrared spectral evidence for compounds of type **111** existing in the oxo form. These same investigators considered structure **112** rather than **113** to represent the predominant tautomeric form of the *O*-methyl derivatives; however, it would be most surprising if this conclusion were correct.

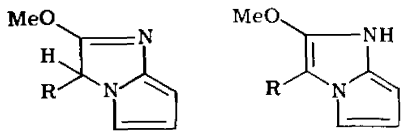
Chemical evidence for the structure of imidazol-4-ones has been summarized,[123] although rather different conclusions would now be drawn from this evidence. For example, in the light of present knowledge, the ease with which imidazol-4-ones react with diazonium salts suggests that an appreciable amount of the 4-hydroxyimidazole exists

[119] D. van der Helm, A. E. Lessor, and L. L. Merritt, *Acta Cryst.* **13,** 1050 (1960).
[120] A. Mustafa and M. M. M. Sallam, *J. Org. Chem.* **26,** 1782 (1961).
[120a] H. Steeple, *Acta Cryst.* **14,** 847 (1961).
[121] H. Kny and B. Witkop, *J. Am. Chem. Soc.* **81,** 6245 (1959).
[122] C. A. Grob and P. Ankli, *Helv. Chim. Acta* **33,** 273 (1950).
[123] K. Hofmann, "Imidazole and Its Derivatives," p. 97. Interscience, New York, 1953.

[*108*] [*109*]

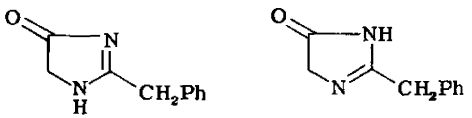


[*110*] [*111*]



[*112*] [*113*]

in solution with acid catalysts present. The isolation both of **114** and of **115** has been claimed,[124] but was later disproved,[125] one of the products having been shown to be a dimer.

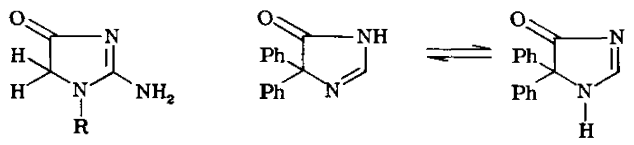


[*114*] [*115*]

Lempert[126] has summerized the considerable speculation on the tautomerism of glycocyanine (**116,** R = H) and creatinine (**116,** R =

[124] H. Finger and W. Zeh, *J. prakt. Chem.* **82,** 50 (1910).
[125] A. Kjaer, *Acta Chem. Scand.* **7,** 1017 (1953).
[126] C. Lempert, *Chem. Revs.* **59,** 667 (1959).

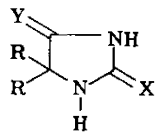
Me), but there is little direct evidence available and no definite conclusions can be drawn. The equilibrium **117** ⇌ **118** appears to favor



[*116*] [*117*] [*118*]

117 on the basis of chemical and ultraviolet spectral evidence,[127,128] but this conclusion has been disputed.[129]

Ultraviolet[127] and infrared spectral data[130,131] indicate that hydantoin and its thio analogs (**119**, X, Y = O or S) exist in the diamide form shown.



[*119*]

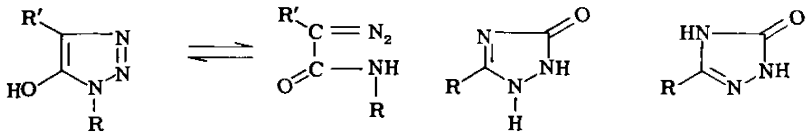
E. Potential Hydroxy Compounds with a Ring System Containing Three or Four Hetero Atoms

Relatively little is known about the complex tautomerism possible in substances of this type, and no general conclusions can yet be formulated.

Hydroxy-1,2,3-triazoles are known, but their detailed structure apparently has not as yet been investigated with respect to their existence in hydroxy or oxo forms. Suitably substituted hydroxy-1,2,3-triazoles (**120**) can undergo another type of tautomerism to give the

[127] H. C. Carrington and W. S. Waring, *J. Chem. Soc.* p. 354 (1950).
[128] H. C. Carrington, C. H. Vasey, and W. S. Waring, *Chem. & Ind. (London)* p. 377 (1954).
[129] J. T. Edward and E. F. Martlew, *Chem. & Ind. (London)* p. 193 (1954).
[130] L. K. Ramachandran, A. Epp, and W. B. McConnell, *Anal. Chem.* **27**, 1734 (1955).
[131] J. Derkosch, *Monatsh. Chem.* **92**, 361 (1961).

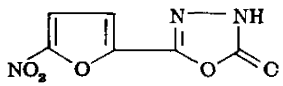
diazoamide **121** (see reference 132 for a review). The infrared and ultraviolet spectra of 1,2,4-triazol-3-one seemed to indicate structure **122**, but it was also claimed that two tautomers (**122** and **123**) could



[*120*] [*121*] [*122*] [*123*]

also be isolated[133]; cf. the discussion in reference 134. It has recently been shown, however, that some of the compounds originally[135] described as hydroxytriazoles are really aminooxadiazoles,[136–139] and structure **123** is preferred for the authentic triazolones on the basis of their infrared spectra.[100a,136,139]

The 1-oxa-3,4-diazol-2-one **124** has been demonstrated to exist in

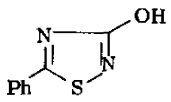


[*124*]

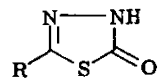
the oxo form shown using infrared spectroscopy.[140]

The hydroxy-1-thia-2,4-diazole **125** is reported to exhibit "phenolic character" and to give a red color with ferric chloride.[141] Infrared[100a,142,143] and ultraviolet spectral evidence[100a] indicates that 1-thia-3,4-diazoles of type **126** exist predominantly in an oxo form.

[132] R. Huisgen, *Angew. Chem.* **72**, 359 (1960).
[133] H. G. Mautner and W. D. Kumler, *J. Am. Chem. Soc.* **77**, 4076 (1955).
[134] H. Gehlen, *Ann. Chem. Liebigs* **563**, 185 (1949).
[135] J. Bougault, *Bull. soc. chim. France* **21**, 246 (1917).
[136] F. Maggio, G. Werber, and G. Lombardo, *Ann. chim. (Rome)* **50**, 491 (1960).
[137] H. Gehlen and G. Blankenstein, *Ann. Chem. Liebigs* **638**, 136 (1960).
[138] K. Futaki and S. Tosa, *Chem. & Pharm. Bull. (Tokyo)* **8**, 908 (1960).
[139] J. C. Howard and H. A. Burch, *J. Org. Chem.* **26**, 1651 (1961).
[140] W. R. Sherman, *J. Org. Chem.* **26**, 88 (1961).
[141] F. Kurzer and S. A. Taylor, *J. Chem. Soc.* p. 3234 (1960).
[142] N. Petri and O. Glemser, *Chem. Ber.* **94**, 553 (1961).
[143] N. Petri and O. Glemser, *Chem. Ber.* **94**, 566 (1961).

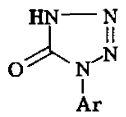


[125]



[126]

A tetrazolone formulation, i.e., structure **127**, has been offered for

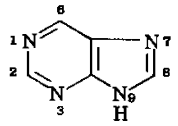


[127]

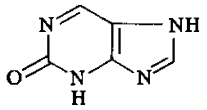
this substituted tetrazole on the basis of infrared (strong C=O absorption) and ultraviolet spectral data.[144,145]

F. Hydroxypurines

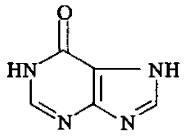
Each of the three monohydroxypurines, i.e., the 2-, 6-, and 8-isomers (cf. **128**), can exist in one or more of four different hydroxy forms in addition to the oxo (or amido) forms; there are five different oxo forms possible for the 2-isomer, four for the 6-isomer, and three for the 8-isomer.[146,147] The presence of a ν C=O band in the infrared spectra of the monohydroxypurines indicates that all three isomers exist predominantly in an oxo form; this band occurs near 1670 cm^{-1} for the 2- and 6-isomers and near 1740 cm^{-1} for the 8-isomer. The infrared spectra of these compounds were also used to distinguish between the *o*-quinonoid (ν NH near 3350 cm^{-1}) and *p*-quinonoid forms (ν NH near 3450 cm^{-1}). On the basis of these data and ultraviolet spectral evidence,[148] the 2-isomer was concluded to exist predominantly as **129** (see also reference 149), the 6-isomer as **130** or **131** (with **130** somewhat more probable) (cf. Section IV,K for the tautomerism of guanine), and the 8-isomer as **132**. The tautomer-



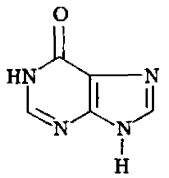
[128]



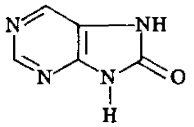
[129]



[130]



[131]



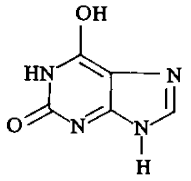
[132]

ism of the hydroxypurines has been discussed from a theoretical point of view,[40,150] and similar theoretical arguments have led to the prediction that 2- and 6-hydroxypurines undergo proton addition at N-7.[42]

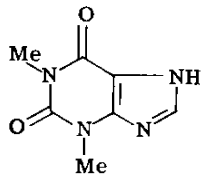
In 1935, structure **133** was proposed for xanthine, analogous structures being suggested for 1-monomethyl- and 3,7-dimethyl-xanthine, but 1,3- (**134**), 1,7-, and 1,9-dimethylxanthine were considered to have dioxo structures (or zwitterion equivalents).[151] These structural differences were proposed to account for the differences in the acid strengths exhibited by these compounds in aqueous and in 90% ethanol solutions; hydroxy acids are known to undergo a larger change in acid strength than "amino acids" under these circumstances. Infrared spectral evidence was later adduced for the existence of theobromine as **135** or **136**.[152] However, it now appears likely that, because

[144] J. P. Horwitz, B. E. Fisher, and A. J. Tomasewski, *J. Am. Chem. Soc.* **81**, 3076 (1959).
[145] J. P. Horwitz, B. E. Fisher, and A. J. Tomasewski, 134th Meeting, Am. Chem. Soc. Abstr., 19P (September 1958, Chicago).
[146] S. F. Mason, *in* "The Chemistry and Biochemistry of Purines" (G. E. W. Wolstenholme and C. M. O'Connor, eds.), p. 60. Little, Brown, Boston, Massachusetts, 1957.
[147] D. J. Brown and S. F. Mason, *J. Chem. Soc.* p. 682 (1957).
[148] S. F. Mason, *J. Chem. Soc.* p. 2071 (1954).
[149] J. J. Fox and D. van Praag, *J. Org. Chem.* **26**, 526 (1961).
[150] B. Pullman and A. Pullman, *Bull. soc. chim. France* p. 973 (1958).
[151] A. G. Ogston, *J. Chem. Soc.* p. 1376 (1935).
[152] E. K. Blout and M. Fields, *J. Am. Chem. Soc.* **72**, 479 (1950).

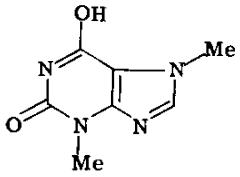
of the similarity between the ultraviolet spectra of xanthine and caffeine (1,3,7-trimethylxanthine), xanthine and all of its derivatives exist in a dioxo form of type **137** provided this form is not precluded.[153,154] The ultraviolet spectrum of xanthine is discussed in



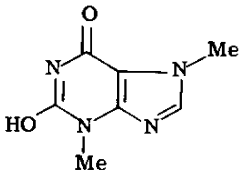
[133]



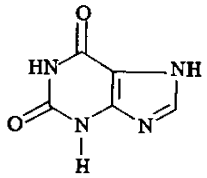
[134]



[135]



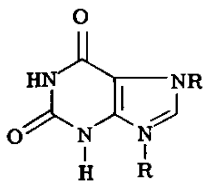
[136]



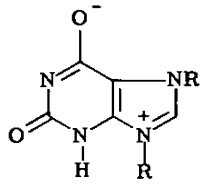
[137]

reference 155.

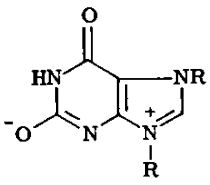
The deoxyuric acids were early formulated with a cyclic triple bond (**138**),[156] but recent chemical evidence and ultraviolet spectral data have led to their reformulation as **139** or **140**.[157] Although the results of the early investigations of the structure of uric acid using chemical methods were interpreted in favor of structure **141**[158-160] and this structure was considered to be supported by its ultraviolet spectrum,[155] it is now known on the basis of ultraviolet spectral comparisons that uric acid exists in the trioxo form **142**.[161-163]



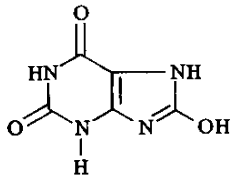
[138]



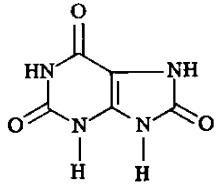
[139]



[140]



[141]



[142]

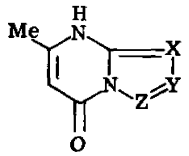
The relation between tautomerism and enzymatic oxidation of various hydroxypurines has been discussed by Bergmann and his associates.[164]

G. Other Polyazaindenes

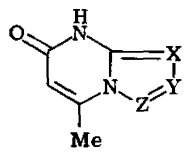
The oxo formulations **143** and **144** (X, Y, Z = N or CH) are supported for this type of compound by infrared and ultraviolet spectral data. With certain substituents in the five-membered ring, forms of type **145** apparently become important,[165] and structure **146** is postulated to predominate on the basis of ultraviolet evidence.[166] Com-

[153] J. R. Loofbourow, M. M. Stimson, and M. J. Hart, *J. Am. Chem. Soc.* **65**, 148 (1943).
[154] L. F. Cavalieri, J. J. Fox, A. Stone, and N. Change, *J. Am. Chem. Soc.* **76**, 1119 (1954).
[155] M. M. Stimson and M. A. Reuter, *J. Am. Chem. Soc.* **65**, 153 (1943).
[156] H. Biltz, *Ann. Chem. Liebigs* **426**, 237 (1922).
[157] H. Bredereck, G. Kupsch, and H. Wieland, *Chem. Ber.* **92**, 566 (1959).
[158] H. Biltz, *Ber. deut. chem. Ges.* **72**, 807 (1939).
[159] H. Biltz, *Ber. deut. chem. Ges.* **69**, 2750 (1936).
[160] H. Biltz, *J. prakt. Chem.* **145**, 65 (1936).
[161] E. Agallidis, H. Fromberz, and A. Hartmann, *Ber. deut. chem. Ges.* **71**, 1391 (1938).
[162] H. Fromberz and A. Hartmann, *Ber. deut. chem. Ges.* **69**, 2420 (1936).
[163] F. Bergmann and S. Dikstein, *J. Am. Chem. Soc.* **77**, 691 (1955).
[164] F. Bergmann, H. Kwietny, G. Levin, and D. J. Brown, *J. Am. Chem. Soc.* **82**, 598 (1960).
[165] C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allen, *J. Org. Chem.* **24**, 779 (1959).
[166] C. C. Cheng and R. K. Robins, *J. Org. Chem.* **21**, 1240 (1956).

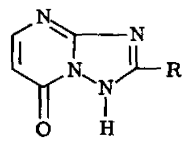
pounds of type **147**[165] and **148**[167] have been formulated as shown on infrared data, and the structure of the triazolopyrimidine **147** (X=Z =N, Y=CH) has been discussed.[168] A report based on infrared spectral data, which are not quoted in detail, that certain pyrazolopyrimidines exist in the hydroxy form (as **149**)[169] is of interest in view of the



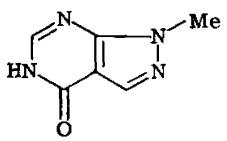
[143]



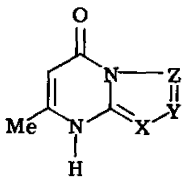
[144]



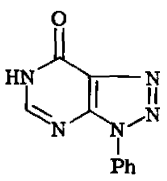
[145]



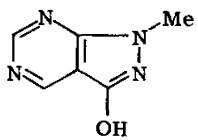
[146]



[147]



[148]



[149]

fact that 1-substituted 3-hydroxypyrazoles exist as such (Section II,A,5).

III. Compounds Containing Potential Mercapto Groups

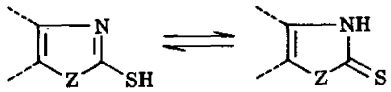
Apparently no data are available for mercapto compounds with hetero atoms-1,2 or for 4-(or 5)-mercapto compounds with hetero atoms-1,3. From the data available, the tautomerism of potential

[167] A. Dornow and J. Helberg, *Chem. Ber.* **93**, 2001 (1960).
[168] V. C. Chambers, *J. Am. Chem. Soc.* **82**, 605 (1960).
[169] M. Hauser, E. Peters, and H. Tieckelmann, *J. Org. Chem.* **26**, 451 (1961).

mercapto compounds appears to resemble that of the corresponding potential hydroxy compounds.

A. Hetero Atoms-1,3

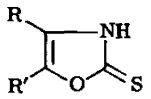
For the most part, only compounds of the type **150** ⇌ **151** have been investigated up to the present, and all the evidence available indicates that they exist predominantly in the thione form (**151**).



[150] [151]

1. *Oxazole-2-thiones*

Oxazole-2-thiones have been shown to exist in the thione form (**152**)



[152]

by comparison of their ultraviolet and fluorescence spectra with those of the *N*- and *S*-alkyl derivatives.[90] Infrared spectroscopic data lead to the same conclusion[91,170] and have also been used to demonstrate the predominance of the thione structure for benzoxazole-2-thione[171] and its nitro derivatives.[172] Zinner and his associates have reported chemical evidence (methylation by diazomethane) for the structure of benzoxazole-2-thiones,[173] but they now consider these data to be equivocal.[172]

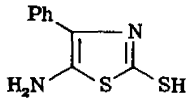
2. *Thiazole-2-thiones*

Although early infrared[174] and chemical data (e.g., reference 175) were interpreted to the contrary, later infrared[100a,171] and ultravio-

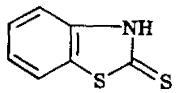
[170] F. Weygand, H. J. Bestmann, and F. Steden, *Chem. Ber.* **91**, 2537 (1958).
[171] M. St. C. Flett, *J. Chem. Soc.* p. 347 (1953).
[172] H. Zinner, R. Reimann, and A. Weber, *Chem. Ber.* **93**, 2035 (1960).
[173] H. Zinner and K. Niendorf, *Chem. Ber.* **89**, 1012 (1956).
[174] H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, "Infrared Determination of Organic Structures." Van Nostrand, New York, 1949.
[175] F. D. Stewart and R. A. Mathes, *J. Org. Chem.* **14**, 1111 (1949).

let spectral evidence[176,177] indicates that thiazole-2-thiones exist in the thione form. Infrared solution spectra show bonded and nonbonded NH absorption bands, the intensities of which vary as expected on dilution.[171] 5-Amino-4-phenylthiazole-2-thione has been reported to exist in the mercapto form **153** on the basis of ultraviolet spectral data,[178] but this report must be viewed with caution.

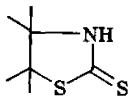
Benzothiazole-2-thiones are associated,[179] but the predominance of the thione forms (**154**, R=H, Me) has been demonstrated by ultraviolet spectral comparisons with the methylated derivatives of both possible tautomeric forms[180,181] (cf. reference 182), comparative dipole moment data,[183] and infrared spectral data.[171] Ultraviolet spectroscopy has also been used to demonstrate that benzoselenazole-2-thione exists as such. The predominance of the thione form of nonaromatic 3,4-dihydrothiazole-2-ones (**155**) has also been established on the basis of ultraviolet spectral evidence.[184]



[*153*]



[*154*]



[*155*]

3. *Imidazole-2-thiones*

The predominance of the thione forms of imidazole-2-thiones[177] and benzimidazole-2-thiones[108] has been established using ultraviolet spectroscopy, and for the former compounds this conclusion is supported by infrared spectroscopic data.[91,101]

B. Compounds with Three or Four Hetero Atoms

The simple monomercapto compounds investigated so far exist in the thiocarbonyl form; evidence for this view is summerized in Table II.

[176] A. J. Beber and R. A. Mathes, *Ind. Eng. Chem.* **41**, 2637 (1949).
[177] A. Lawson and H. V. Morley, *J. Chem. Soc.* p. 1103 (1956).
[178] E. S. Stern, *J. Chem. Soc.* p. 1664 (1949).
[179] G. Hopkins and L. Hunter, *J. Chem. Soc.* p. 638 (1942).
[180] R. A. Morton and A. L. Stubbs, *J. Chem. Soc.* p. 1321 (1939).
[181] C. Hasan and R. F. Hunter, *J. Chem. Soc.* p. 1672 (1936).
[182] H. P. Koch, *J. Chem. Soc.* p. 401 (1949).
[183] P. F. Oesper, G. L. Lewis, and C. P. Smyth, *J. Am. Chem. Soc.* **64**, 1130 (1942).
[184] D. O. Holland and P. Mamalis, *J. Chem. Soc.* p. 4588 (1958).

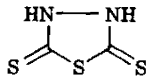
TABLE II
Evidence for the Thiocarbonyl Formulation

Positions of hetero atoms				Position of C=S group	Technique	References
1	2	3	4			
O	—	NH	N	2	IR	*a,b,c,d*
S	—	NH	N	2	IR	*d,e,f,g,h*
N	NH	—	NPh	3	UV	*i*
S	N	N	NH	5	IR	*j*
NR	N	N	NH	5	IR	*k*
					UV + p*K*	*l*

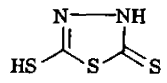
[a] C. Ainsworth, *J. Am. Chem. Soc.* **78**, 4475 (1956).
[b] R. W. Young and K. H. Wood, *J. Am. Chem. Soc.* **77**, 400 (1955).
[c] W. R. Sherman, *J. Org. Chem.* **26**, 88 (1961).
[d] S. V. Sokolov and I. Ya. Postovskiĭ, *Zhur. Obshcheĭ Khim.* **30**, 1781 (1960); *Chem. Abstr.* **55**, 7399 (1961).
[e] C. Ainsworth, *J. Am. Chem. Soc.* **80**, 5201 (1958).
[f] G. Pala, *Ann. chim. (Rome)* **49**, 1464 (1959).
[g] N. Petri and O. Glemser, *Chem. Ber.* **94**, 566 (1961).
[h] N. Petri and O. Glemser, *Chem. Ber.* **94**, 553 (1961).
[i] G. A. Reynolds and J. A. van Allen, *J. Org. Chem.* **24**, 1478 (1959).
[j] E. Lieber, C. N. Pillai, J. Ramachandran, and R. D. Hites, *J. Org. Chem.* **22**, 1750 (1957).
[k] E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran, and R. D. Hites, *Can. J. Chem.* **36**, 801 (1958).
[l] E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.* **37**, 563 (1959).

The tautomerism of certain difunctional derivatives of 1-thia-3,4-diazole has received considerable attention. Pala[185] assigned structure **156** to 2,5-dimercapto-1-thia-3,4-diazole on the basis of infrared spectral data, and Thorn[186] reached the same conclusion by comparing its ultraviolet spectrum (measured in ethanol) with those of the four possible methylated derivatives. However, the infrared spectrum of a chloroform solution of the parent compound showed bands at 2600–2550 cm^{-1} indicating an SH group and the probable occurrence of form **157** under these conditions,[186] and this conclusion is supported by the occurrence of SH bands in solid state spectra obtained by Swiss investigators.[72] For a summary of earlier work on these compounds, see reference 187.

[185] G. Pala, *Ann. chim. (Rome)* **49**, 1464 (1959).
[186] G. D. Thorn, *Can. J. Chem.* **38**, 1439 (1960).
[187] L. L. Bambas, "Five-Membered Heterocyclic Compounds with Nitrogen and Sulfur or Nitrogen, Sulfur, and Oxygen," p. 185. Interscience, New York, 1952.



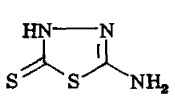
[156]



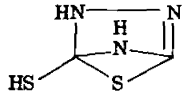
[157]

Janniah and Guha[188,189] reported that 2-amino-1-thia-3,4-diazol-5-thione (**158**) exists in two forms; the sterically-unacceptable bridged structure **159** was postulated for one of these forms. Bambas[190] suggests instead that the two forms may be the individual tautomers **160** and **161**. The second explanation is hardly more probable than the first, and the whole problem needs reinvestigation. Certain related compounds with a substituted-amino group have been shown by ultraviolet spectral comparisons to exist in the thione form.[190a]

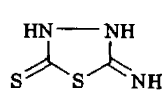
The tautomeric equilibria **162** ⇌ **163** ⇌ **164** have been discussed.[191] The infrared spectra show the presence of a C=O group in this sys-



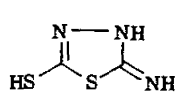
[158]



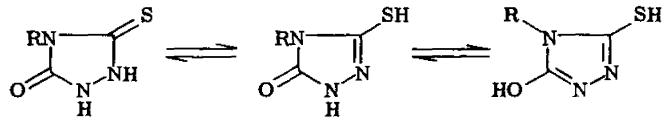
[159]



[160]



[161]



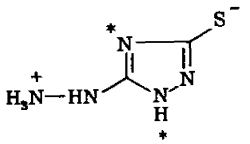
[162] [163] [164]

tem, but it was concluded that chemical evidence favored structure **163** rather than **162**. Early investigators postulated that sterically-unacceptable bridged ring structures participated in the tautomerism of

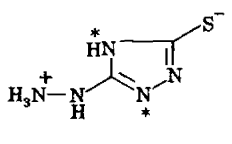
[188] S. L. Janniah and P. C. Guha, *J. Am. Chem. Soc.* **52**, 4860 (1930).
[189] S. L. Janniah and P. C Guha, *J. Indian Inst. Sci.* **16A**, 11 (1933); *Chem. Abstr.* **27**, 3711 (1933).
[190] L. L. Bambas, "Five-Membered Heterocyclic Compounds with Nitrogen and Sulfur or Nitrogen, Sulfur, and Oxygen," p. 151. Interscience, New York, 1952.
[190a] K. Arvidsson and J. Sandström, *Acta Chem. Scand.* **15**, 1179 (1961).
[191] M. Tišler, *Arch. Pharm.* **292**, 90 (1959).

these compounds.[192,193] A reinvestigation of these compounds using physical methods would be welcome.

Accurate X-ray crystallographic data indicate that 5-hydrazino-3-mercapto-1,2,4-triazole exists in the solid state as a betaine, either as **165** or **166**, with strong intermolecular hydrogen bonding occurring be-



[165]

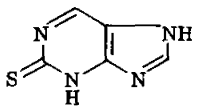


[166]

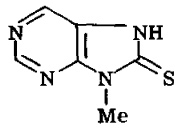
tween the two starred atoms.[193a]

C. Mercaptopurines

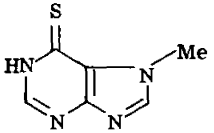
2-Mercaptopurine probably exists in a thione form (e.g., **167**) since its ultraviolet spectrum is different from that of 2-(methylthio)purine.[148] Purine-2-thione and its 6-amino derivative were assigned thione structures on the basis of their infrared spectra.[194] 8-Mercapto-9-methyl- and 6-mercapto-7-methyl-purine exist at least partially in thione forms, presumably **168** and **169**, respectively, since their in-



[167]



[168]

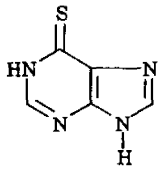


[169]

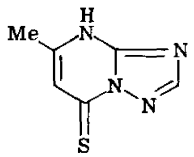
frared spectra contain a ν NH band; however, bands which may or may not be due to ν S—H are also present.[147] Ultraviolet spectral comparisons with the 1-, 3-, 6-, 7-, and 9-methyl derivatives show

[192] M. Busch and E. Opfermann, *Ber. deut. chem. Ges.* **37**, 2333 (1904).
[193] S. Nirdlinger and S. F. Acree, *Am. J. Chem.* **44**, 219 (1910).
[193a] M. E. Senko and D. H. Templeton, *Acta Cryst.* **11**, 808 (1958).
[194] C. H. Willits, J. C. Decius, K. L. Dille, and B. E. Christensen, *J. Am. Chem. Soc.* **77**, 2569 (1955).

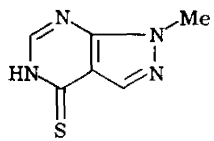
that purine-6-thione exists predominantly as **170**,[195] and thione formulations for **171**[165] and **172**[166] are also supported by ultraviolet spec-



[170]



[171]



[172]

troscopy (cf. also reference 195a). The infrared and ultraviolet spectra of other purinethiones have been discussed.[146]

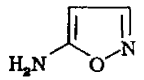
The tautomerism of purine-6-thione has also been discussed in relation to its enzymatic oxidation.[196]

IV. Compounds Containing Potential Amino Groups

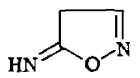
It is now clear that the great majority of compounds containing potential amino groups exist in the amino form, although relatively little quantitative data are currently available and several discrepancies still await elucidation. As is always the case, the tendency for an amino compound to exist in the corresponding imino form is less than the tendency for a hydroxy compound to tautomerize to the oxo form.

A. Aminoisoxazoles

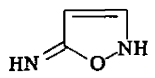
The amino structure **173** was suggested for 5-aminoisoxazoles rather than the imino structure **174** on the basis of tentative chemical data and evidence from the exaltation of the molecular refractivity[197,198]; however, forms of type **175** were not taken into consideration in these



[173]



[174]



[175]

[195] G. B. Elion, *in* "Ciba Foundation Symposium on the Chemistry and Biology of Purines" (G. E. W. Wolstenholme and C. M. O'Connor, eds.), p. 39. Little, Brown, Boston, Massachusetts, 1957.

[195a] I. L. Doerr, I. Wempen, D. A. Clarke, and J. J. Fox, *J. Org. Chem.* **26**, 3401 (1961).

[196] F. Bergmann and H. Ungar, *J. Am. Chem. Soc.* **82**, 3957 (1960).

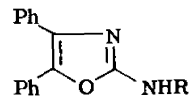
[197] K. v. Auwers and H. Wunderling, *Ber. deut. chem. Ges.* **67**, 638 (1934).

[198] K. v. Auwers, T. Bahr, and E. Frese, *Ann. Chem. Liebigs* **441**, 68 (1925).

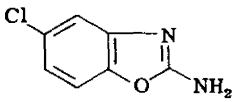
investigations. Recently, detailed consideration of the infrared and nuclear magnetic resonance spectra of representative 3-, 4-, and 5-aminoisoxazoles has shown that these compounds exist essentially completely in the amino form.[199,200]

B. Aminooxazoles

The predominance of the amino structure has been demonstrated for **176** (R = Ph, CH_2Ph) by ultraviolet spectral comparisons with both types of alkylated derivatives.[201] Similarly, comparison of the ultraviolet spectra of 2-amino-5-chlorobenzoxazole (**177**) and its



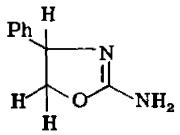
[176]



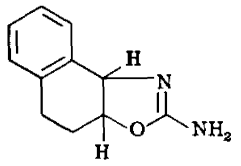
[177]

methylated derivatives led to the conclusion that the former existed as an amino compound in solution; however, infrared spectral data were considered to suggest the predominance of the imino forms of these compounds in the solid state,[202] which seems unlikely. The amino formulation has been proposed for 2-aminobenzoxazole[203,204] on the basis of chemical evidence.

Investigation[205] of oxazoline derivatives using infrared spectroscopy and pK measurements showed that the amino forms **178** and **179**



[178]



[179]

[199] A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta* **17**, 238 (1961).

[200] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 51 (1961).

[201] R. Gompper and F. Effenberger, *Chem. Ber.* **92**, 1928 (1959).

[202] J. Sam, J. N. Plampin, and G. I. Poos, *J. Org. Chem.* **23**, 1500 (1958).

[203] R. D. Desai, R. F. Hunter, and A. R. K. Khalidi, *J. Chem. Soc.* p. 321 (1938).

[204] R. D. Desai, R. F. Hunter, and A. R. K. Khalidi, *J. Chem. Soc.* p. 1186 (1934).

[205] J. Pitha, J. Jonáš, J. Kovář, and K. Bláha, *Collection Czechoslov. Chem. Communs.* **26**, 834 (1961).

predominate over the tautomer with an exocyclic imino group both in polar and in nonpolar solvents. In aqueous media K_T values of about 10–20 were found.

C. Aminothiazoles

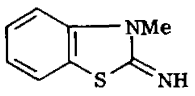
The ultraviolet and infrared spectra of 2-aminothiazole and the methyl derivatives of both the imino and the amino forms have been compared and discussed by Sheĭnker, Kushkin, and Postovskiĭ[206] who showed that the amino form predominates in the solid state and in various solvents. The reaction of 2-aminothiazoles with methyl iodide in the presence or in the absence of sodium ethoxide has been considered to give information concerning the proportion of the amino and imino forms present under these conditions.[207]

Similarly, for 2-(*p*-substituted-anilino)benzothiazoles (**180** ⇌ **181**), the relative proportions of the isomeric *N*-methyl derivatives produced on reaction with methyl iodide in neutral solution has been related to

[*180*] [*181*]

the influence of X (R has little effect) on the position of the tautomeric equilibrium between **180** and **181**.[207,208] Chemical evidence of this type has also been reported for 2-amino- and 2-anilino-benzoselenazole.[209] Other investigators[210,211] have interpreted chemical evidence to indicate that 2-aminobenzothiazoles exist in the imino form. Polarographic comparison of 2-aminobenzothiazole with **182**, however, showed that the former exists predominantly in the amino form,[212] and ultraviolet and infrared spectral data substantiate this conclusion.[213]

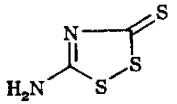
[206] Yu. N. Sheĭnker, V. V. Kushkin, and I. Ya. Postovskiĭ, *Zhur. Fiz. Khim.* **31**, 214 (1957).
[207] R. F. Hunter, E. R. Parken, and E. M. Short, *J. Chem. Soc.* p. 784 (1959).
[208] R. F. Hunter, E. R. Parken, and E. M. Short, *J. Chem. Soc.* p. 1561 (1958).
[209] C. Hasan and R. F. Hunter, *J. Chem. Soc.* p. 1762 (1935).
[210] R. Q. Brewster and F. B. Dains, *J. Am. Chem. Soc.* **58**, 1364 (1936).
[211] T. Wagner-Jauregg and E. Helmert, *Ber. deut. chem. Ges.* **75**, 935 (1942).
[212] F. von Sturm and W. Hans, *Angew. Chem.* **67**, 743 (1955).
[213] G. Costa, *Ann. chim.* (*Rome*) **43**, 585 (1953).



[*182*]

On the basis of chemical evidence, it has been suggested that 2,4-diaminothiazoles do not exist in the diamino form.[214]

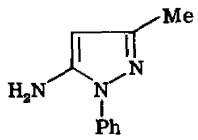
The aminodithiazole derivative **182a** exists as shown on the basis of X-ray evidence.[214a]



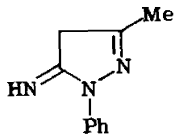
[*182a*]

D. Aminopyrazoles

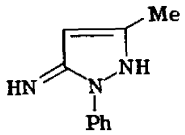
Italian investigators[215,216] have discussed the tautomerism of 5-amino-3-methyl-1-phenylpyrazole in terms of structures **183** and **184** (**185** was not considered) and appear to be of the opinion that reaction



[*183*]



[*184*]



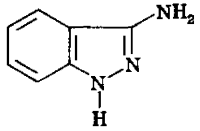
[*185*]

with reagents such as nitrous acid and sulfonyl chlorides to give 4-substituted compounds indicates the predominance of the imino form

[214] J. M. Sprague and A. H. Land, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. V, p. 614. Wiley, New York, 1957.
[214a] A. Hordvik, *Acta Chem. Scand.* **15**, 1186 (1961).
[215] G. B. Crippa and M. Guarneri, *Gazz. chim. ital.* **85**, 199 (1955).
[216] S. Checchi, M. Ridi, and P. Papini, *Gazz. chim. ital.* **85**, 1558 (1955).

184. The opposite conclusion has been reached for similar compounds,[217] but the evidence offered is not convincing. Although definite evidence is not yet available, the present authors feel that simple aminopyrazoles probably exist largely in the amino form (cf. 183). More complex aminopyrazoles have been assigned the amino structure by Taylor and Hartke[218,219] on the basis of chemical, infrared, and ultraviolet spectral data.

Aron and Elvidge[220] have pointed out that the occurrence of absorption bands at 3448 and 3306 cm^{-1} in the infrared spectrum of 3-aminoindazole suggests that it does, indeed, exist in the amino form (186) (cf. also reference 221).



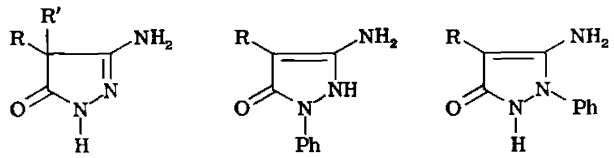
[186]

E. Aminopyrazolones

3-Aminopyrazol-5-ones, which can exist in as many as ten different tautomeric forms,[222] have been extensively investigated by Gagnon and his co-workers.[83,222-227] Some of their initial interpretations[222] were later partially withdrawn[227] because incorrect structural assignments had been made. From arguments based on chemical reactivity and ultraviolet spectral data, pyrazolones which show a low intensity absorption peak at a high wavelength were concluded to be probably of the $\Delta^{2,3}$ type or to contain a 3-imino group, whereas those pyrazolones which exhibit a high intensity peak at a short wavelength were

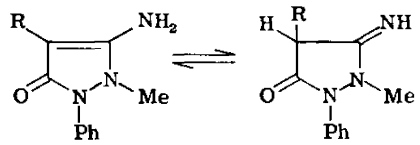
[217] H. Beyer, T. Pyl, and K. Wünsch, *Chem. Ber.* **93**, 2209 (1960).
[218] E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2456 (1959).
[219] E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2452 (1959).
[220] M. A. Aron and J. A. Elvidge, *Chem. & Ind. (London)* p. 1234 (1958).
[221] F. C. Cooper, *J. Chem. Soc.* p. 4212 (1958).
[222] P. E. Gagnon, J. L. Boivin, and R. N. Jones, *Can. J. Research* **27B**, 190 (1949).
[223] P. E. Gagnon, J. L. Boivin, P. A. Boivin, and R. N. Jones, *Can. J. Chem.* **29**, 182 (1951).
[224] P. E. Gagnon, J. L. Boivin, and A. Chisholm, *Can. J. Chem.* **30**, 904 (1952).
[225] P. E. Gagnon, J. L. Boivin, and J. Giguere, *Can. J. Chem.* **29**, 328 (1951).
[226] P. E. Gagnon, B. Nolin, and R. N. Jones, *Can. J. Chem.* **29**, 843 (1951).
[227] P. E. Gagnon, J. L. Boivin, and R. N. Jones, *Can. J. Research* **28B**, 34 (1950).

thought to contain a double bond between positions 3 and 4.[223,226] The ionization constants of these compounds have also been discussed with respect to the tautomeric equilibria involved.[83] For each of the following types of compounds, the predominant tautomeric form was considered to be represented by structures **187** (R′ = H),[225] **188**,[224] and **189**.[223] The ultraviolet spectra of **187** (R = R′ = alkyl) and **187**



[187] [188] [189]

(R = alkyl, R′ = H) are similar. These conclusions cannot be accepted without reservation since there was sometimes confusion in this work between the processes of tautomerism and ionization. Other investigators considered both structures **190** and **191** to be important on tenuous chemical grounds.[228]

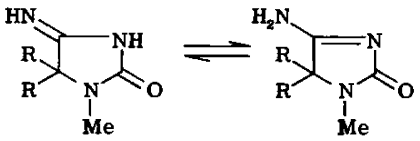


[190] [191]

F. Aminoimidazoles

Only equivocal chemical evidence appears to be available for the unsubstituted aminoimidazoles. The failure of 2-aminoimidazole to undergo diazotization was originally interpreted to indicate that it existed in the imino form[229]; more recently, the 4-amino analog has been reported to behave as a normal aromatic amine.[230] The infrared spectra of substituted aminoimidazoles of type **192** ⇌ **193** were con-

[228] H. Stenzl, A. Staub, C. Simon, and W. Baumann, *Helv. Chim. Acta* **33**, 1183 (1950).
[229] R. G. Fargher and F. L. Pyman, *J. Chem. Soc.* **15**, 217 (1919).
[230] G. Hunter and J. A. Nelson, *Can. J. Research* **19B**, 296 (1941).

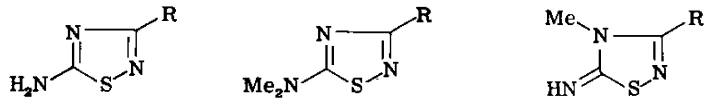


[192] [193]

sidered to suggest that the imino form **192** predominates[231]; however, chemical evidence has been reported to favor the predominance of the amino structure (**193**).[232] All these compounds need reinvestigation.

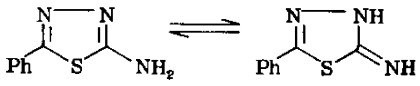
G. Aminothiadiazoles

The structure of 5-amino-1-thia-2,4-diazoles has been clarified by Goerdeler, Huppertz, and Wember[233] who compared the ultraviolet spectra and basicities of **194** (R = Me or Ph) and the methylated derivatives **195** and **196**, thereby showing that **194** exists in the amino form. This conclusion is supported by polarographic data.[212]



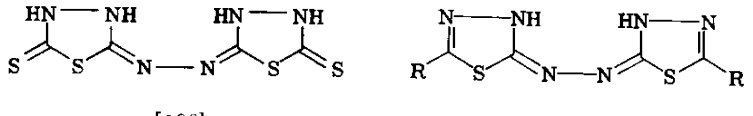
[194] [195] [196]

Substituted 2-amino-1-thia-3,4-diazoles have been studied by Testa *et al.*[234] Comparison of ultraviolet and infrared spectra of the parent compound (**197** ⇌ **198**) with those of its four possible methylated derivatives indicated that **197** predominates in aqueous solution and



[197] [198]

[231] A. F. McKay, G. Y. Paris, and D. L. Garmaise, *J. Am. Chem. Soc.* **80**, 6276 (1958).
[232] R. M. Herbst and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 3676 (1930).
[233] J. Goerdeler, A. Huppertz, and K. Wember, *Chem. Ber.* **87**, 68 (1954).
[234] E. Testa, G. G. Gallo, F. Fava, and G. Weber, *Gazz. chim. ital.* **88**, 812 (1958).

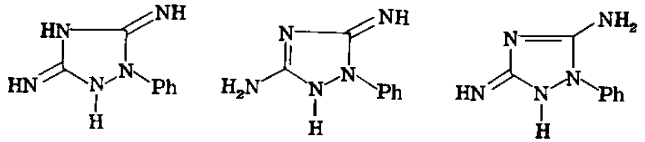


[199] [200]

in the solid state. Polarographic data support this conclusion, and basicity measurements show that forms of type **197** are favored by a factor of about 10^5. 2-Anilino- and 2-amino-1-thia-3,4-diazole have also been assigned amino-type structures on the basis of ultraviolet spectral comparisons[235] and infrared spectral data,[185] respectively. However, ultraviolet spectral data were considered to indicate that dithia- and diaryl-hydrazino derivatives exist in the diimino forms **199** and **200**, respectively.[143] Other amino-1-thia-3,4-diazoles have been discussed.[236]

H. Aminotriazoles

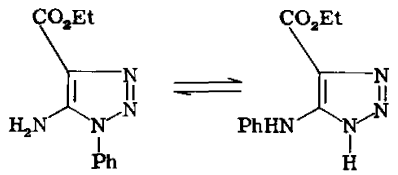
Fragmentary ultraviolet spectral data are available for 3-amino-1,2,4-triazole.[237] Early chemical data on 3,5-diamino-2-phenyl-1,2,4-triazole were interpreted on the basis of the diimino structure **201**,[238] but ultraviolet spectral evidence was later stated to favor either structure **202** or **203**.[239,240]



[201] [202] [203]

At elevated temperatures, some 5-amino-1,2,3-triazoles can undergo reversible isomerization of the type **204** ⇌ **205** (for a review see reference **132**).

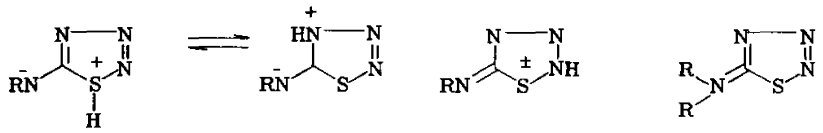
[235] B. Stanovnik and M. Tišler, *J. Org. Chem.* **25**, 2234 (1960).
[236] R. Stollé and K. Fehrenbach, *J. prakt. Chem.* **122**, 289 (1929).
[237] B. G. van den Bos, *Rec. trav. chim.* **79**, 1129 (1960).
[238] G. Pellizzari, *Gazz. chim. ital.* **24**, 481 (1894).
[239] E. A. Steck and F. C. Nachod, *J. Am. Chem. Soc.* **79**, 4411 (1957).
[240] E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.* **80**, 3929 (1958).



[204] [205]

I. Aminothiatriazoles

Zwitterion structures (**206** ⇌ **207** ⇌ etc.) as well as the "mesoionic structure" **208** have been proposed for these compounds.[241] The exact significance of structure **208** and the term "mesoionic" is unclear in



[206] [207] [208] [209]

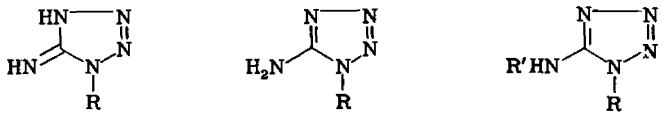
this context (cf. definition given in reference 242) and justifies the concern expressed regarding the misuse of this term.[243] Infrared[244] and ultraviolet spectral data[245] are stated to be in accord with the "mesoionic formulation," but the similarity of the dipole moments of 5-amino-, 5-methylamino-, and 5-dimethylamino-thiatriazole has been taken to indicate that these compounds exist in the amino form **209**,[245] and this is supported by proton resonance spectroscopy.[245a] The present authors feel that there is no convincing evidence for the predominance of form **206**, **207**, or **208**.

J. Aminotetrazoles

In 1951, aminotetrazoles were reported to exist in the imino form **210** rather than in the amino form (**211**) on the basis of chemical

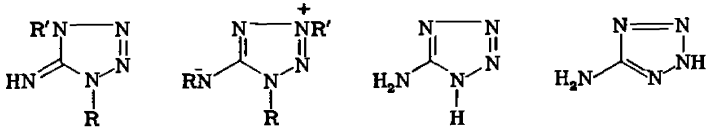
[241] E. Lieber, C. N. Pillai, and R. D. Hites, *Can. J. Chem.* **35**, 832 (1957).
[242] N. J. Leonard and D. M. Locke, *J. Am. Chem. Soc.* **77**, 1852 (1955).
[243] A. R. Katritzky, *Chem. & Ind. (London)* p. 521 (1955).
[244] E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran, and R. D. Hites, *Can. J. Chem.* **36**, 801 (1958).
[245] E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.* **37**, 563 (1959).
[245a] G. Englert, *Z. anal. Chem.* **181**, 447 (1961).

evidence[246] which is rather unconvincing. Alkylation was initially reported to give products which are more strongly basic than the parent compounds and were thought to be of type **212**. The structure of these alkylation products, however, was later corrected to **213**,[247]



[210] [211] [212]

the basicity differences thus indicating that the parent compounds exist in the amino form (**211**). This conclusion is supported by the fact that the ultraviolet spectrum of **211** (R = H) is different from that of **213** (R = Me).[248] Similarly, the amino structure of aminotetrazole appears to be compatible with its infrared spectrum,[248,249] and X-ray crystallographic data are apparently in agreement with the formulation of 2-methyl-5-aminotetrazole as such.[250] Ultraviolet spectral evidence has been advanced as a basis for formulation of aminotetrazoles in the betaine form **214**,[251] but no comparison was made with fixed derivatives of forms **215** and **216**.



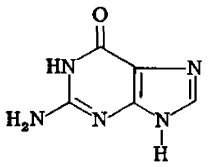
[213] [214] [215] [216]

K. Aminopurines

Early ultraviolet spectral data on adenine were interpreted to indicate that amino–imido tautomerism occurs,[252] but the similarity be-

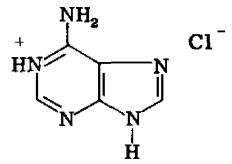
[246] R. M. Herbst, C. W. Roberts, and E. J. Harvill, *J. Org. Chem.* **16**, 139 (1951).
[247] R. M. Herbst and D. F. Percival, *J. Org. Chem.* **19**, 439 (1954).
[248] D. B. Murphy and J. P. Picard, *J. Org. Chem.* **19**, 1807 (1954).
[249] E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.* **23**, 1594 (1951).
[250] J. H. Bryden, *Acta Cryst.* **9**, 874 (1956).
[251] R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.* **76**, 2894 (1954).
[252] J. R. Loofbourow and M. M. Stimson, *J. Chem. Soc.* p. 844 (1940).

tween the ultraviolet spectra of monoaminopurines and their dimethylamino analogs was later suggested to show that all of these compounds exist in the amino form.[148] The infrared spectra of 9-ethyl-6-aminopurine[146] and of adenine and various of its derivatives[253] are also in accord with amino formulations. The infrared spectrum of guanine supports its formulation as **217**.[253]



[*217*]

After inconclusive early work,[254] structure **218** was demonstrated for adenine hydrochloride using X-ray diffraction[255] (cf. also reference 256) and was later supported by nuclear magnetic resonance evidence.[257] Four possible structures have been advanced for guanine



[*218*]

hydrochloride on the basis of X-ray crystallographic data,[256] and nuclear magnetic resonance spectroscopic studies indicate that guanine undergoes N-7 protonation.[257] Theoretical studies[42] have led to the suggestion that adenine, 2-aminopurine, and 8-aminopurine should protonate at N-1, but that 2,6-diaminopurine should protonate principally at N-3.

[253] C. L. Angell, *J. Chem. Soc.* p. 504 (1961).
[254] J. M. Broomhead, *Acta Cryst.* **1**, 324 (1948).
[255] W. Cochran, *Acta Cryst.* **4**, 81 (1951).
[256] J. M. Broomhead, *Acta Cryst.* **4**, 92 (1951).
[257] C. D. Jardetzky and O. Jardetzky, *J. Am. Chem. Soc.* **82**, 222 (1960).

V. Acylaminoazoles

Compounds of this type were investigated by Sheĭnker and his collaborators[258] (cf. reference 259) following their work on the analogous six-membered ring compounds (see Volume 1, article II, Section V,A), and their findings are summarized in Table III. The trichloroacetyl and trifluoroacetyl compounds exist in the imino form in the solid

TABLE III
VALUES OF LOG K_T = LOG (IMINO/AMINO) CALCULATED FROM SPECTROSCOPIC DATA[a]

Ring system and substituent	Solid[b]	Solvent			
		H_2O	EtOH	Dioxane	C_6H_{14}
2-Thiazole					
—$COCH_3$	A	—	—	—	—
—$COCHCl_2$	A	0.7	−0.7	−1.1	—[c]
—$COCCl_3$	I	—	0.7	0.2	−1.5
—$COCF_3$	I	—	—	—	—
2-Benzothiazole					
—$COCH_3$	A	—	—	—	—
—$COCHCl_2$	A	—	−0.6	1.0	—
—$COCCl_3$	I	—	0.9	0.3	−1.1
2-(1-Thia-3,4-diazole)					
—$COCH_3$	A	—	—	—	—
—$COCHCl_2$	A	0.2	−0.4	−0.7	—
—$COCCl_3$	A + I	—[d]	—[d]	1.8	−0.7

[a] Data taken from Yu. N. Sheĭnker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* **33**, 2096 (1959).
[b] A and I indicate the predominance of the amino and imino forms, respectively.
[c] K_T is too small to measure.
[d] K_T is too large to measure.

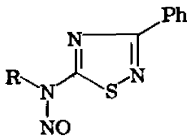
state and predominantly so in solution, the importance of the imino form decreasing as the dielectric constant of the solvent decreases. Infrared spectral studies have shown that representative 2-, 3-, and 4-acetamidoisoxazoles exist as such,[199,200] whereas the amino formula-

[258] Yu. N. Sheĭnker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, *Zhur. Fiz. Khim.* **33**, 2096 (1959) [English translation: *Russian J. Phys. Chem.* **33**, 303 (1959)].
[259] I. Ya. Postovskiĭ and I. B. Lundina, *Zhur. Obshcheĭ Khim.* **29**, 608 (1959); *Chem. Abstr.* **54**, 1499 (1960).

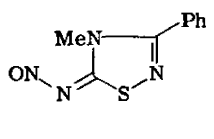
tion has been advanced for 2-acylaminooxazoles on the basis of chemical evidence.[260]

VI. Nitrosoamino, Nitramino, Sulfonamido, and Hydrazino Compounds

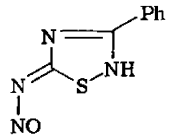
5-Nitrosamino-3-phenyl-1-thia-2,4-diazole was assigned structure **219** (R = H) by comparison of its ultraviolet spectrum with those of compounds **219** (R = Me) and **220** in which the double bond is fixed



[*219*]



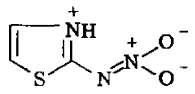
[*220*]



[*221*]

in an endocyclic or exocyclic position, respectively[261]; however, the tautomeric form represented by structure **221** was not taken into consideration.

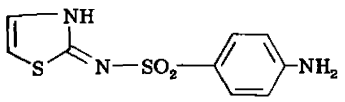
The zwitterionic structure **221a** was assigned to 2-nitroaminothiazole since its infrared spectrum contained a broad band at 3200 cm^{-1} which was considered to be the ν $\overset{+}{N}$—H frequency.[261a]



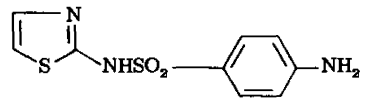
[*221a*]

Relatively little data are available on sulfonamido derivatives of heterocyclic systems with five-membered rings.[261b] The tautomeric equilibrium between structures **222** and **223** has been shown to favor the imine form by about 10:1 by comparison of the ultraviolet spectrum of the parent compound with those of both methylated forms.[262]

[260] J. W. Cornforth, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. V, p. 335. Wiley, New York, 1957.
[261] J. Goerdeler and K. Deselaers, *Chem. Ber.* **91**, 1025 (1958).
[261a] A. Taurins, *Can. J. Chem.* **36**, 465 (1959).
[261b] H. Dorn, G. Hilgetag, and A. Rieche, *Angew. Chem.* **73**, 560 (1961).
[262] R. G. Shepherd, A. C. Bratton, and K. C. Blanchard, *J. Am. Chem. Soc.* **64**, 2532 (1942).



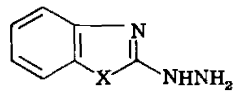
[*222*]



[*223*]

Sheĭnker and his co-workers[263] have used ultraviolet and infrared spectroscopic data to show that the imino form of benzenesulfonamido derivatives of thiazoles and 1-thia-3,4-diazoles is preferred to the amino form by a large factor. In view of this work, the formulation of 2-arylsulfonamidooxazoles in the amino form on the basis of chemical evidence[260] must be regarded with caution.

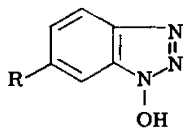
Available pK data[264] indicate that hydrazino compounds of type **224** exist predominantly as such.



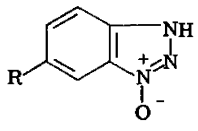
[*224*]

VII. Compounds with Potential *N*-Oxide Groups

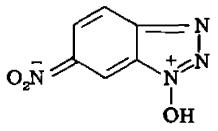
Macbeth and Price[265] have shown that in ethanolic solution the tautomeric equilibrium between **225** and **226** is about 80% in favor of the hydroxy form (**225**) when R is H and that the equilibrium is shifted still further toward the hydroxy form when R is NO_2 by comparison of the ultraviolet spectra of the parent compounds and



[*225*]



[*226*]



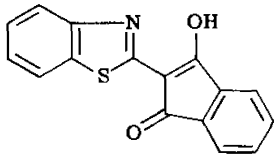
[*227*]

[263] Yu. N. Sheĭnker, I. Ya. Postovskiĭ, N. M. Voronina, and V. V. Kushkin, *Zhur. Fiz. Khim.* **31**, 1745 (1957).
[264] S. Hünig and H. Balli, *Ann. Chem. Liebigs* **628**, 56 (1959).
[265] A. K. Macbeth and J. R. Price, *J. Chem. Soc.* p. 111 (1936).

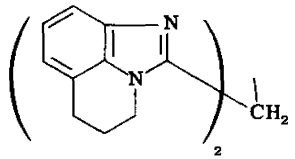
their alkylated derivatives. When R is NO_2, canonical form **227** would be expected to stabilize structure **225** giving rise to the observed shift in the equilibrium position.

VIII. Potential Methyl or Substituted Methyl Compounds

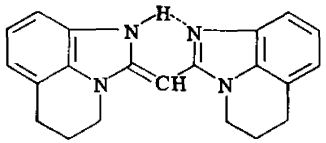
The simple methyl compounds do indeed contain methyl groups, e.g., methylthiazoles exist as such and not in the methylene form.[206] The structures of compounds of the pyrophthalone type containing a benzimidazole and benzthiazole nucleus, e.g. **228**, have been discussed.[266] Bis(benzimidazolyl)methanes (**229**) absorb light in the



[228]



[229]



[230]

visible region of the spectrum indicating that they exist at least partly in a methine form (**230**).[108]

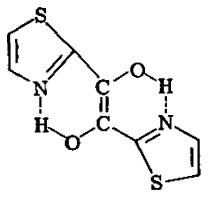
IX. Miscellaneous

Infrared spectral data show that thiazoloin exists in the hydrogen bonded ene-diol form **231** (cf. α-pyridoin, in Volume 1, article II, Section VI,F).

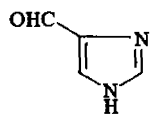
The existence of imidazole-4-aldehyde (**232**) in the "enolic" form **233** was postulated on the basis of chemical evidence,[267] but the infrared spectrum indicates the presence of a carbonyl group and absence of a hydroxyl group, suggesting that structure **232** should

[266] D. G. Manly, A. Richardson, A. M. Stock, C. H. Tilford, and E. M. Amstutz, *J. Org. Chem.* **23**, 373 (1958).

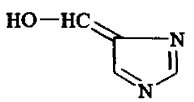
[267] W. Hubball and F. L. Pyman, *J. Chem. Soc.* p. 21 (1928).



[231]



[232]



[233]

be assigned to this compound.[268] Ultraviolet spectral evidence also supports structure **232**.

[268] R. A. Turner, *J. Am. Chem. Soc.* **71**, 3472 (1949).

Three-Membered Rings with Two Hetero Atoms

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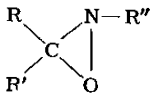
I. Introduction

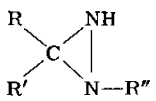
Three-membered rings with *one* hetero atom were known in the 19th century. Today they are of great interest, both scientifically and technically. Because of ring strain, they are energy-rich compounds comparable with cyclopropane.

The unfavorable ring-strain energy is usually not apparent in the rate of formation of three-membered rings. In fact, the formation of three-membered rings is often easier than the closure of open chains to larger rings, and many syntheses of three-membered ring systems occur under surprisingly mild conditions. Hence, it might be expected that three-membered rings with *two* hetero atoms could also be formed.

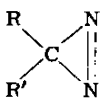
Thus it is not surprising that three-membered rings with two hetero atoms were mentioned in the literature at an early stage. For example, at the turn of the century, nitrones, hydrazones, and aliphatic diazo compounds were all formulated with three-membered rings (**1**, **2**, **3**). Later the three-membered ring structures for these compounds became questionable. The structure of the aliphatic diazo compounds was studied very intensively. For diazomethane no clas-



(1)



(2)



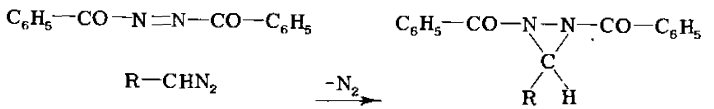
(3)

sical valence bond formula except for the three-membered ring can be given; a satisfactory linear structure for diazomethane could only be formulated with the development of the theory of mesomerism. The discussion of the linear canonical forms of diazomethane was of special importance both in the clarifying of its reactions and in the development of the theory of mesomerism. However, an unambiguous negation of the three-membered ring formula for diazomethane cannot be obtained by chemical means.

Confirmation of the linear arrangement came by physical techniques, especially electron diffraction and infrared spectroscopy.[1] Later the nonequivalence of the nitrogen atoms in diazoacetic ester was shown by means of N^{15} labeling.[2]

The discussion of the structure of the nitrones and the hydrazones received less attention. With the increased application of physical methods to structural problems, the three-membered ring structures for these compounds lost much of their attraction. The problem of the structure of the nitrones was satisfactorily solved with the open-chain *N*-oxide formulation. The compounds originally designated as diaziridines (**2**) were partly reformulated with the open-chain hydrazone structures and partly were left without a satisfactory proof of structure.

In a recent review of heterocyclic compounds no further mention is made of the three-membered ring structures for the condensation products from hydrazine and carbonyl compounds.[3] However, the products obtained from azodicarbonyl derivatives with aliphatic diazo compounds[4] were formulated as diaziridines [Eq. (1)]. Recent investi-



(1)

[1] For references see R. Huisgen, *Angew. Chem.* **67**, 439 (1955).
[2] K. Clusius and U. Lüthi, *Helv. Chim. Acta* **40**, 445 (1957).
[3] E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IV-A, p. 20. Elsevier, Amsterdam, 1957.
[4] E. Müller, *Ber. deut. chem. Ges.* **47**, 3001 (1914); H. Staudinger and A. Gaule, *ibid.* **49**, 1961 (1916).

gations have not confirmed the three-membered ring structure for these compounds.[5] It now is apparent that *up to the year 1950 no three-membered ring with two hetero atoms had been prepared.*

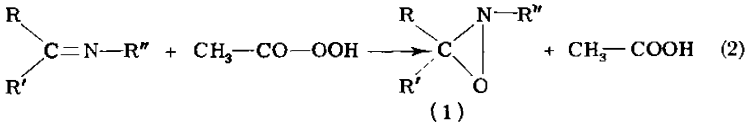
In the last 10 years many three-membered rings with two hetero atoms have been synthesized. Their formation occurs surprisingly smoothly with an ease comparable to that of the three-membered rings with one hetero atom. The oxaziranes (**1**), diaziridines (**2**), and diazirines (**3**) have become, in a very short time, classes of compounds with an extensive literature.

II. Oxaziranes

A. Preparation of Oxaziranes

1. *Preparation of Oxaziranes from Schiff's Bases and Peracids*

Oxaziranes (**1**) are produced by the action of peracids on Schiff's bases [Eq. (2)], a reaction first described by Krimm in patents.[6]



(2)

Krimm named the compounds as isonitrones. Independently of Krimm's work, the same reaction was discovered by Emmons[7,8] and Horner and Jürgens.[9]

The preparation of oxaziranes is almost always carried out by reacting a solution of peracetic acid in a volatile inert solvent at temperatures near 0°C with the Schiff's base. Without any significant variation in the reaction conditions, a large number of oxaziranes has thus been prepared. Table I gives a selection of the fifty or so known oxaziranes.

The wide range of applicability of the reaction can be seen from Table I. Formaldehyde, aliphatic aldehydes, and aromatic and hetero-

[5] E. Fahr, *Angew. Chem.* **73**, 536 (1961); R. Breslow, C. Yaroslawsky, and S. Yaroslawsky, *Chem. & Ind. London* p. 1961 (1961).
[6] H. Krimm and K. Hamann (Farbenfabriken Bayer A.G.) German Patent 952,895 (July 11, 1952); German Patent 959,094 (Oct. 30, 1952); Brit. Patent 743,940 (July 9, 1953); H. Krimm, K. Hamann, and K. Bauer, U. S. Patent 2,686,739 (July 13, 1953).
[7] W. D. Emmons, *J. Am. Chem. Soc.* **78**, 6208 (1956).
[8] W. D. Emmons, *J. Am. Chem. Soc.* **79**, 5739 (1957).
[9] L. Horner and E. Jürgens, *Chem. Ber.* **90**, 2184 (1957).

aromatic aldehydes can be brought into reaction in the form of their Schiff's bases, and so can aliphatic and cycloaliphatic ketones. For the amine component, aliphatic amines predominate. However, in

TABLE I
OXAZIRANES FROM SCHIFF'S BASES AND PERACIDS[a]

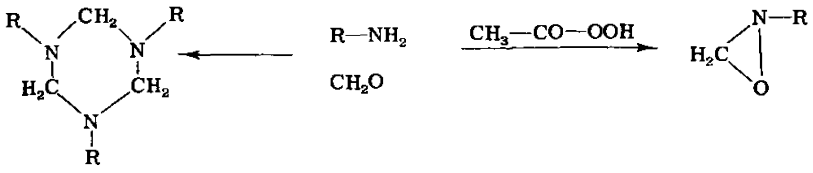
Schiff's bases from		Yield of oxazirane		
Carbonyl compound	Amine	(%)	Bp (°C)/mm	Ref.
Formaldehyde	*t*-Butylamine	46	52–54/75	8
Acetaldehyde	Isobutylamine	53	40–42/32	10
Butyraldehyde	Isopropylamine	71	43–45/13	10
Isobutyraldehyde	α-Phenylethylamine	80	—	8
Benzaldehyde	Cyclohexylamine	80	mp. 47°C	9
Furfural	Methylamine	53	44–46/0.6	10
Pyridine-2-aldehyde	*t*-Butylamine	75	68–70/0.4	8
Acetone	Isopropylamine	59	58–59/60	10
Diethyl ketone	Ethylamine	56	62/19	8
Methyl isobutyl ketone	*n*-Propylamine	73	61/8	8
Cyclopentanone	Cyclohexylamine	87	74–76/0.4	10
Cyclohexanone	*p*-Chloroaniline	89	mp. 69–70°C	10
Glyoxal	*t*-Butylamine	51[b]	mp. 42–43°C	8
			mp. 82–84°C	8
Terephthalic dialdehyde	Ethylamine	45[b]	mp. 93°C	9
Cyclohexanone	Ethylenediamine	39[b]	mp. 106–107°C	10

[a] Corresponds to Eq. (2).
[b] The compound contains two oxazirane rings.

principle it is quite possible to use Schiff's bases derived from aromatic amines. In all cases yields of oxaziranes of 40–90% were obtained.

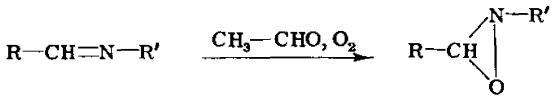
The process can be still more simplified. It is not always necessary to use a pre-formed Schiff's base. Often it is sufficient to bring the carbonyl compound and the amine together in an inert solvent and to add the peracid to the mixture later.[6,9] In this way oxaziranes can be obtained in good yield even if the Schiff's base is unknown or can only be obtained in poor yield. For example, formaldehyde gives with aliphatic amines usually only trimers of the Schiff's bases (**4**). On the other hand, the synthesis of 2-cyclohexyl-oxazirane (**5**) from cyclohexylamine, formaldehyde, and peracetic acid proceeded in 66%

[10] H. Krimm, *Chem. Ber.* **91**, 1057 (1958).



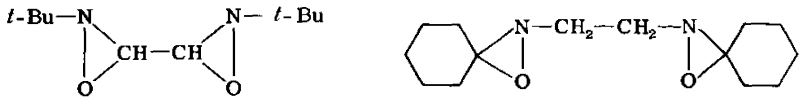
(4) (5): R = C_6H_{11}

yield.[10] A further simplification is possible because a peracid can be obtained by aerial oxidation of an aldehyde [Eq. (3)].[11]



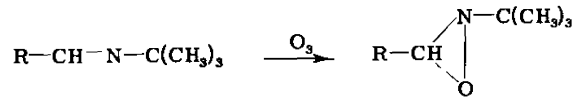
(3)

Compounds which contain two oxazirane rings are obtainable from Schiff's bases of glyoxal or terephthalic dialdehyde, e.g. (**6**).[8] A bifunctional oxazirane is also obtained from ethylene diamine and cyclohexanone (**7**).[10]



(6) (7)

Isolated reports have appeared of the use of other sources of oxygen for the synthesis of oxaziranes. Belew and Person[12] obtained an oxazirane (**8**) by the reaction of ozone on isobutylidene-*tert*-butyl-



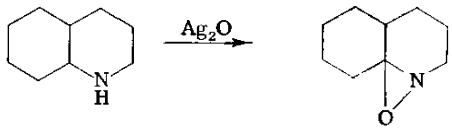
(4)

(8): R = *i*-Pr
(9): R = C_6H_5

[11] H. Krimm and H. Schnell (Farbenfabriken Bayer A.G.), German Patent 1,061,784 (Dec. 2, 1957).
[12] J. S. Belew and J. T. Person, *Chem. & Ind. (London)*, p. 1246 (1959).

amine [Eq. (4)]. Bailey and co-workers[13] obtained 2-*tert*-butyl-3-phenyloxazirane (**9**) from benzylidene-*tert*-butylamine and ozone.

According to a report by Japanese authors, oxazirane rings are also formed by the action of silver oxide on perhydro–nitrogen heterocycles, e.g., decahydroquinoline (**10**) [Eq. (5)].[14]

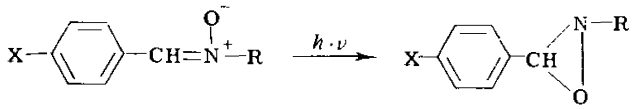


(5)

(10)

2. *The Preparation of Oxaziranes by the Irradiation of Nitrones*

The light sensitivity of nitrones in solution was observed by Kamlet and Kaplan,[15] who postulated the formation of oxaziranes. Kröhnke formulated the rearrangement caused by light on a nitrone by using an oxazirane as an intermediate.[16] Splitter and Calvin[17] successfully isolated the rearranged products (**9**, **11**, **12**) and identified them as known oxaziranes [Eq. (6)].



(6)

(9): X = H; R = *t*-Bu

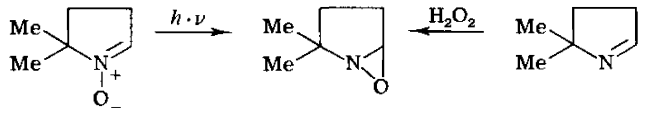
(11): X = NO_2; R = *t*-Bu

(12): X = NO_2; R = Et

The rearrangement of phenyl-*tert*-butyl nitrone to the isomeric oxazirane (**9**) occurred in 95% yield on irradiation in acetonitrile for 2 hr. Because 2-*tert*-butyl-3-phenyloxazirane (**9**) can be reconverted into the more stable nitrone, the photochemical reaction involves the conversion of radiation energy into chemical energy.

[13] A. H. Riebel, R. E. Erickson, C. J. Abshire, and P. S. Bailey, *J. Am. Chem. Soc.* **82**, 1801 (1960).
[14] N. Katsui and Y. Ichinohe, *Bull. Chem. Soc. (Japan)* **32**, 787 (1959).
[15] M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.* **22**, 576 (1957).
[16] F. Kröhnke, *Ann.* **604**, 203 (1957).
[17] J. S. Splitter and M. Calvin, *J. Org. Chem.* **23**, 651 (1958).

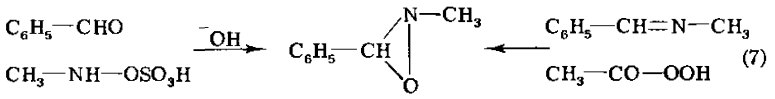
The same rearrangement was observed somewhat later by the irradiation of 5,5-dimethyl-Δ^1-pyrroline oxide (**13**).[18] The product (11% yield) was shown to be identical with the oxazirane (**14**) synthesized from 5,5-dimethyl-Δ^1-pyrroline and hydrogen peroxide.



(13) (14)

3. *The Preparation of Oxaziranes from Carbonyl Compounds and Derivatives of Hydroxylamine and Chloramine*

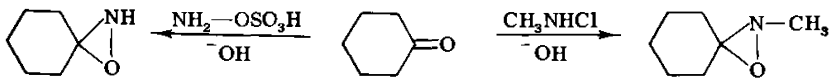
Mixtures of benzaldehyde, *N*-methylhydroxylamine-*O*-sulfonic acid and dilute sodium hydroxide react to give oxaziranes [Eq. (7)].[19] The 2-methyl-3-phenyloxazirane (**15**) obtained (40% yield) is identical with the product synthesized by Krimm[10] from benzylidenemethylamine and peracetic acid. The reaction is completed at 0°C within 1 min, and therefore it can successfully compete with the alkaline decomposition of the oxazirane. With respect to the carbonyl component this reaction is hardly limited: acetone, cyclohexanone, acetophenone, butyraldehyde, and *m*-nitrobenzaldehyde all react normally.



(7)

(15)

Reaction of hydroxylamine-*O*-sulfonic acid with cyclohexanone in alkaline solution can be shown to give pentamethyleneoxazirane (**16**).[19] Compound **16** is an isomer of cyclohexanone oxime. It decomposes even at room temperature and thus cannot be prepared in a pure state.



(16) (17)

[18] R. Bonnett, V. M. Clark, and A. R. Todd, *J. Chem. Soc.* p. 2102 (1959).
[19] E. Schmitz, R. Ohme, and D. Murawski, *Angew. Chem.* **73**, 708 (1961).

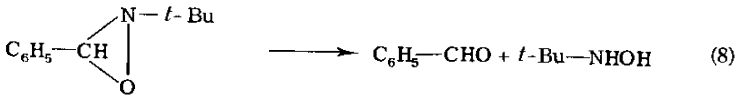
N-Chloromethylamine attacks ketones in alkaline solution with formation of oxaziranes[19]; with cyclohexanone, compound **17** is produced in 50% yield. The reaction with aldehydes with *N*-chloromethylamine yields predominantly acid amides.[20] However, oxaziranes are also produced here as by-products. From benzaldehyde and *N*-chloromethylamine, 2-methyl-3-phenyloxazirane (**15**) was obtained in 10% yield.

B. Properties and Proof of Structure of Oxaziranes

The oxaziranes are in the majority of cases distillable liquids with boiling points somewhat higher than the corresponding Schiff's bases. During distillation, temperatures above 100°C should be avoided. In distinction to the isomeric nitrones, the less polar oxaziranes are usually noncrystalline. They have a characteristic unpleasant smell and are nonbasic. Attempts to force salt formation results in fission of the three-membered ring.[8]

The oxaziranes are colorless and they do not absorb in the UV region. Aryl-substituted oxaziranes show only the absorption of the aryl group. The oxaziranes are also transparent in the double bond region of the infrared spectrum, but they show a well developed band near 1400 cm^{-1} which has been considered characteristic for oxaziranes.[10]

The UV and IR spectra eliminate structures with a CN double bond. The isomerism of nitrones and oxaziranes thus cannot be a result of *cis* or *trans* arrangement of substituents about a double bond. The carbon atoms of an oxazirane are still at the oxidation level of the carbonyl compound used in its syntheses. By acid hydrolysis, for example, 2-*tert*-butyl-3-phenyloxazirane (**9**) can be split into benzaldehyde and *tert*-butylhydroxylamine [Eq. (8)].[8]



(9) (8)

Thus the structure of the oxazirane must formally involve elimination of water from one molecule each of the carbonyl compound and of an alkyl hydroxylamine. (In the synthesis of oxazirane from *N*-methylhydroxylamine-*O*-sulfonic acid and benzaldehyde,[19] this method

[19] E. Schmitz, *Angew. Chem.* 73, 23 (1961).

of building up the molecule is realized.) Because dimeric structures can be eliminated, the only possibility remaining is the CON three-membered ring.

The nuclear magnetic resonance (NMR) spectra of 2-*tert*-butyloxazirane and 2-*tert*-butyl-3-phenyloxazirane (**9**) are in agreement with the three-membered ring formula.[8] The first shows two peaks (oxazirane and *tert*-butyl protons). The latter shows in addition a third peak (phenyl protons). The absorption of the oxazirane proton is split by higher resolution into two peaks because of the *cis* or *trans* relation to the alkyl group on the neighboring tetrahedral nitrogen atom. This splitting shows that rapid inversion of the substituent on the nitrogen does not take place.[21]

The molecular refraction of oxaziranes is in accordance with the values calculated from the individual refractions. For the isomeric nitrones, exaltation occurs.[10]

Two pieces of chemical evidence support the three-membered ring formulation. The bifunctional oxazirane prepared from glyoxal, *tert*-butylamine, and peracetic acid (**6**) can be obtained in two crystalline isomeric forms.[8] According to the three-membered ring formula there should be two asymmetric carbon atoms which should allow the existence of *meso* and *racemic* forms. A partial optical resolution was carried out with 2-*n*-propyl-3-methyl-3-isobutyloxazirane.[8] Brucine was oxidized to the *N*-oxide with excess of the oxazirane. It was found that the unused oxazirane was optically active.

Further indications of the structure of the oxaziranes are obtained by reduction and isomerization. None of the reactions described in the following sections is incompatible with the three-membered ring structure.

C. Reactions of Oxaziranes

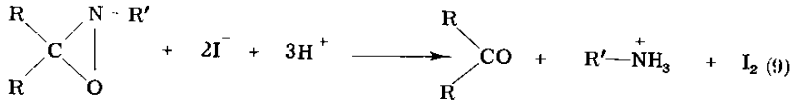
The oxaziranes show their high-energy content in their reactions, which, without exception, involve the opening of the three-membered ring, whether they involve reducing agents, acids, alkalies, radical reagents, or oxidizing agents. The components thus obtained (e.g., carbonyl compounds and amines) often react further to form ill-defined secondary products. The clarification of these reactions was mainly carried out by Emmons[8] who defined the individual reactions,

[21] See also footnote 15 in A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.* 80, 5203 (1958).

determined the nature of the products, and proposed reaction mechanisms.

1. *Reductive Fission of Oxaziranes*

The most characteristic property of the oxaziranes is their strong oxidizing character which is approximately equal to that of hydrogen peroxide. Oxaziranes react with hydrochloric acid; the chlorine thus liberated is, however, used up in secondary reactions.[10] Two equivalents of iodine are formed from acid iodide solutions according to Eq. (9).[8-10] Titration of the free iodine allows a simple estimation of



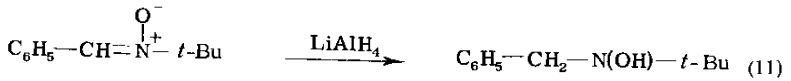
(9)

oxaziranes. In all cases 92–100% of the calculated quantity of iodine was set free. In addition, the three equivalents of acid used up according to Eq. (9) can be determined by back-titration with alkali. This allows differentiation from other oxidizing agents. After an iodimetric titration, the carbonyl compound and amine can be separately characterized or isolated in form of their Schiff's base.

Similarly the active oxygen of oxaziranes can be transferred to triphenylphosphine with the formation of phosphine oxide[9] and to tertiary amines yielding amine oxides.[8]

Reduction with lithium aluminum hydride allows a differentiation from the isomeric nitrones.[8] Whereas 2-*tert*-butyl-3-phenyloxazirane (9) gives benzylidene-*tert*-butylamine [Eq. (10)], reduction of the isomeric nitrone leads to *N*-benzyl-*N*-*tert*-butylhydroxylamine [Eq.

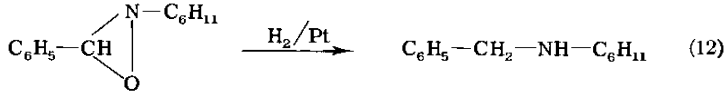
(10)



(11)

(11)]. Thus, 2-*tert*-octyloxazirane was reduced directly to the secondary amine.[8] The catalytic hydrogenation also led to the secondary amine in the case of the 2-cyclohexyl-3-phenyloxazirane [Eq. (12)],[9]

whereas the isomeric nitrone was reduced to the disubstituted hydroxylamine [Eq. (13)].



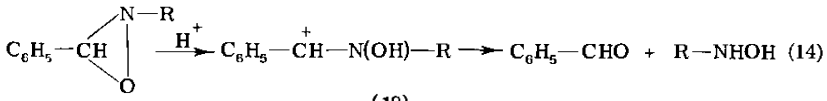
(12)

(13)

2. *Fission of Oxaziranes by Acids*

The behavior of oxazirane toward acids could not be predicted from the experience with other classes of compounds. Oxaziranes possess an astonishing resistance even toward strong acid. In this respect they show a clear difference from *N,O*-acetals or compounds which contain an OCN group in a larger ring.

Here a typical property of three-membered rings with two hetero atoms is shown and this property is also found in the diaziridines. Only with the oxaziranes which are substituted by aryl groups in the 3-position does the hydrolysis by acids occur according to Eq. (14) with formation of an aromatic aldehyde and alkyl hydroxylamine.



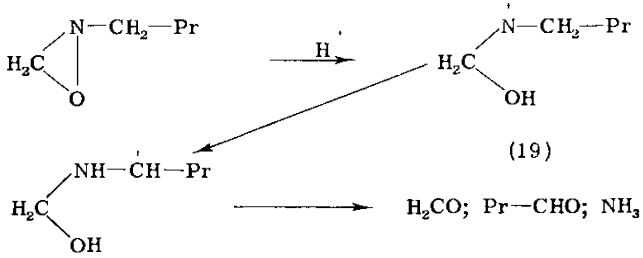
(14)

(18)

The acid-catalyzed hydrolysis of 3-aryloxaziranes is a useful process for the syntheses of alkyl hydroxylamines. Emmons[8] prepared, e.g., *tert*-butylhydroxylamine in 82% yield and *tert*-octylhydroxylamine in 86% yield; Horner and Jürgens[9] obtained cyclohexylhydroxylamine in 70% yield.

According to Emmons[8] an intermediate stage of the hydrolysis is the protonated nitrone (18). In the transition state of the ring opening there must be a significant partial positive charge on the carbon atom. Smooth hydrolysis is only possible if a positive charge on the C-atom is stabilized by the substituents. In the aryl-substituted oxaziranes the positive charge is formed in the benzyl position.

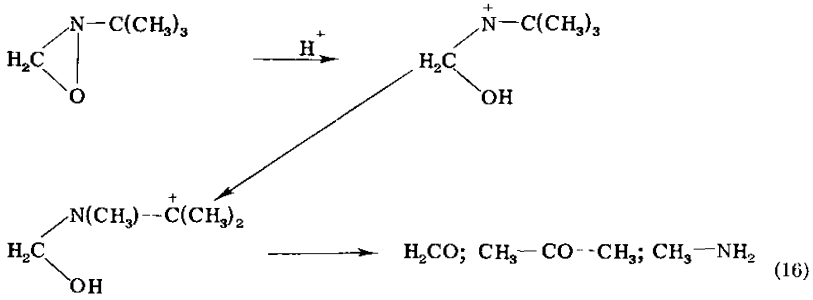
With the aliphatic-substituted oxaziranes the assistance of the substituent for the hydrolysis is lost. Therefore they are decomposed by the action of acids in another manner. The action of methanolic sulfuric acid on 2-*tert*-octyloxazirane gave a small amount of *tert*-nitrooctane as the only defined product according to Emmons.[6] In the presence of 2,4-dinitrophenylhydrazine, which trapped the carbonyl compounds formed, the reaction process became clarified. In all the cases investigated one carbonyl compound was formed from the alkyl group attached to the nitrogen atom. Thus 2-*n*-butyloxazirane gave quantitatively formaldehyde and *n*-butyraldehyde, with 0.79 mole of ammonia [Eq. (15)]. Probably during the ring opening an electron



(19) (15)

sextet was formed on nitrogen (**19**). The electron deficiency on nitrogen was satisfied by the shift of a hydride ion from the neighboring carbon atom.

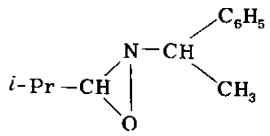
If no hydrogen atom is available in the position next to the nitrogen sextet, an alkyl group shifts. In the action of acid on 2-*tert*-butyloxazirane a methyl shift occurs [Eq. (16)]. Formaldehyde



(16)

and acetone were obtained quantitatively as the 2,4-dinitrophenylhydrazones, and methylamine itself in 67% yield.[8]

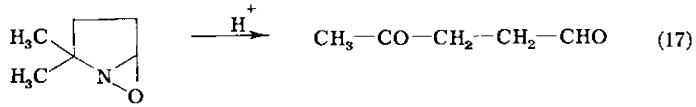
A 1–2-phenyl shift occurs especially easily. In the acid fission of 2-(α-phenylethyl)-3-isopropyloxazirane (**20**) aniline was isolated as the sole basic fission component. Of the two available groups,



(20)

methyl and phenyl, only the phenyl group shifts. Thus the following series of decreasing tendency to shift is found: phenyl > H > alkyl.[8]

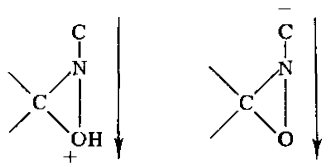
The acid fission of the bicyclic oxazirane **14** to levulinic aldehyde [Eq. (17)][18] is a further example of a dealkylation involving a methyl shift.



(14) (17)

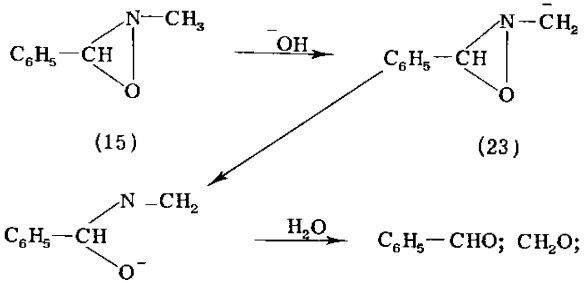
3. *Alkaline Fission of Oxaziranes*

The rupture of the oxazirane ring at the ON-bond occurring with acid treatment of the alkyl-substituted compounds is probably the result of an electronic shift initiated by the protonated oxygen (arrows as in **21**). In principle, a similar rearrangement of the electronic system should also be possible initiated from the nitrogen end (**22**). Indeed, decomposition products similar to those of the



(21) (22)

acid fission are obtained when suitable oxaziranes are treated with alkalies.[8] The reaction [Eq. (18)] can be explained by assuming anion formation in the α-position to the ring nitrogen (**23**). Dealkylation at nitrogen occurs with simultaneous ring opening. The N-alkyl group is converted to a carbonyl compound. The final products, two



(15) (23)

$$C_6H_5-CH(O)-N(-CH_2)-CH_2^- \xrightarrow{H_2O} C_6H_5-CHO;\ CH_2O;\ NH_3 \quad (18)$$

carbonyl compounds and ammonia, correspond to an acid catalyzed fission with a hydrogen shift. For example 2-methyl-3-phenyloxazirane (**15**) decomposes by the action of alkali with the formation of ammonia (0.80 mole), benzaldehyde (0.91 mole), and formaldehyde (0.71 mole) [Eq. (18)].

The action of potassium hydroxide on a solution of 2-(α-phenylethyl)-3-isopropyloxazirane (**20**) in glycol solution gives a mixture of acetophenone (0.25 mole), isobutyraldehyde (0.57 mole), and ammonia (0.92 mole).[8]

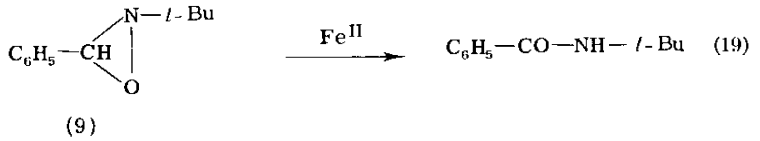
The almost quantitative formation of free ammonia can be used for an estimation of the oxazirane.[8] With pure oxaziranes, ammonia yields of 93–96% are obtained.

In agreement with the proposed mechanism, N-*tert*-alkyl-substituted oxaziranes are stable toward alkali. 2-*tert*-Butyl-3-phenyloxazirane (**9**) is not attacked by standing at room temperature with sodium methoxide solution for 12 hr. Thus, the oxazirane ring itself does not react with basic reagents.

4. *Fission of the Oxazirane Ring with Ferrous Salts*

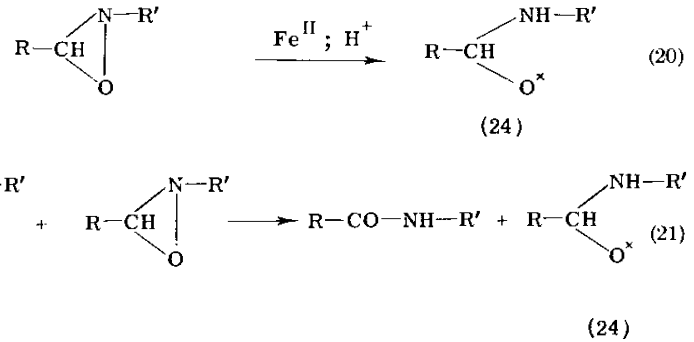
A direct attack on the oxazirane ring occurs with ferrous salts.[8] Oxaziranes are decomposed by aqueous solutions of ferrous ammonium sulfate even at room temperature. The reaction follows a radical-chain mechanism because less than stoichiometric amounts of the ferrous salt cause the decomposition. 2-*tert*-Butyl-3-phenyloxazirane (**9**) and 1 equivalent of ferrous salt give *tert*-butylbenzamide in 98%

yield [Eq. (19)]. Using 0.1 equivalent of ferrous salt, the yield of the amide was 68%, the residue being unaltered oxazirane.



(9)

Emmons[8] proposes as the chain starting reaction a direct attack of the ferrous ion on the oxazirane ring with the formation of an O-radical (**24**) [Eq. (20)]. This radical (**24**) starts a reaction chain [Eq. (21)]. By the attack of a further molecule of oxazirane, forma-



(24) (24)

tion of the acid amide occurs with the re-formation of radical **24** which carries on the chain. By the continuation of the chain finally only hydrogen from radical **24** is transferred to the oxazirane. The course of the reaction is homogeneous.

Much more complicated is the course of the reaction if the oxazirane is derived instead of from benzaldehyde from an aliphatic ketone. Here the possibility of an H-transfer does not occur. Further complications are found if the N-alkyl group can be attacked by the radicals.

In the reaction of 2,3,3-triethyloxazirane (**25**), three radicals are involved: **26**, **27**, and **28**. Radical **26** (Fig. 1) corresponds to the chain reaction propagating radical of the previously mentioned decomposition [Eqs. (20) and (21)]. From **26** by fragmentation an ethyl radical (**27**) is formed together with the acid amide. Finally, by radical attack on the oxazirane, **29** can be formed which rearranges to the

radical **28**. The considerable amounts of ammonia which form during the reaction indicate such a radical dealkylation at nitrogen. The three radicals **26**, **27**, and **28** start radical chain reactions. The ethyl radical thus gives ethane; radical **28** attacks C—H bonds yielding

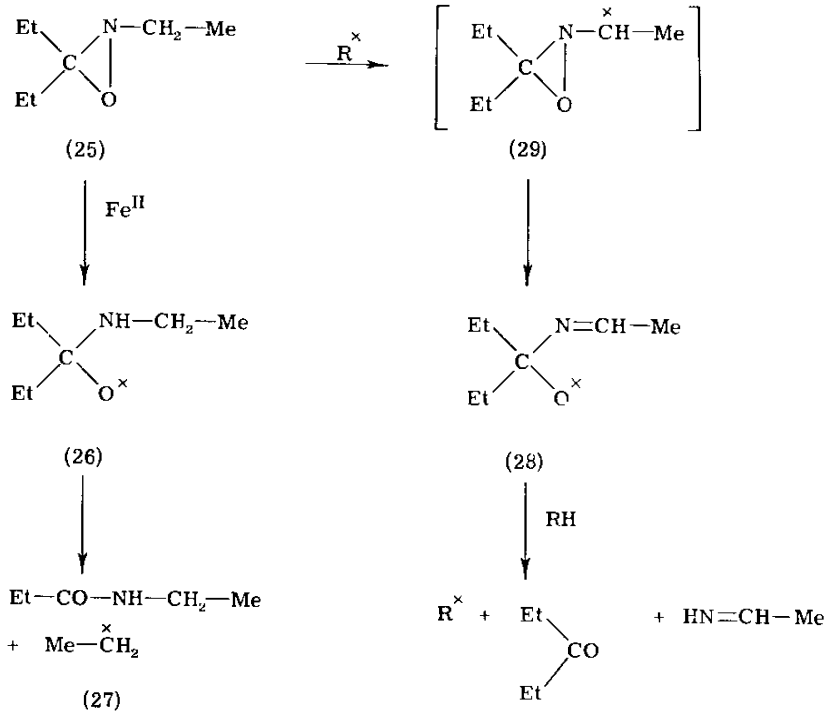
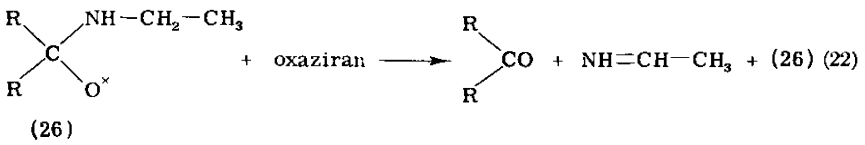


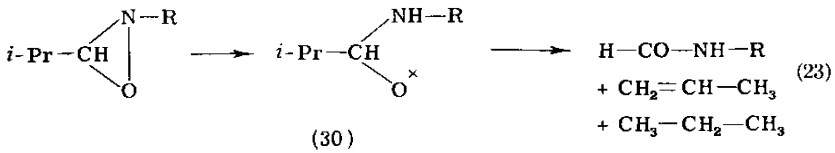
FIG. 1. Fission of 2,3,3-triethyloxazirane by ferrous salts.

diethyl ketone and ammonia. By the attack of **26** on the *N*-alkyl group of the oxazirane, diethyl ketone and ammonia are also formed according to Eq. (22). From this reaction 0.5 mole of diethyl ketone,



0.32 mole of *N*-ethylpropionamide, and 0.55 mole ammonia were isolated.

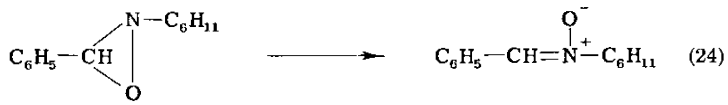
Oxaziranes derived from isobutyraldehyde react with ferrous salts to give only substituted formamides [Eq. (23)]. The chain propagating radical **30** thus suffers fission with elimination of the isopropyl group. An H-transfer would lead to substituted butyramides, which are not found. Here is seen a parallel to the fragmentation of alkoxyl radicals,[22] where the elimination of an alkyl group is also favored over hydrogen. The formulation of the oxazirane fission by a radical mechanism is thus supported.



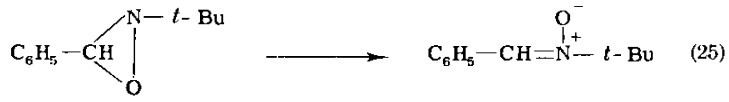
5. *Pyrolysis and Thermal Decomposition of Oxaziranes*

Most oxaziranes withstand temperatures of 100°C for a short time, e.g., on distillation. At higher temperatures isomerization and decomposition occur. Oxaziranes derived from aromatic aldehydes are here again differentiated from the alkyl-substituted oxaziranes.

a. Isomerization to Nitrones. 2-Cyclohexyl-3-phenyloxazirane isomerizes on heating to 200°C. With further increase in temperature it is converted into *N*-cyclohexylbenzaldoxime (70%) [Eq. (24)].[9]



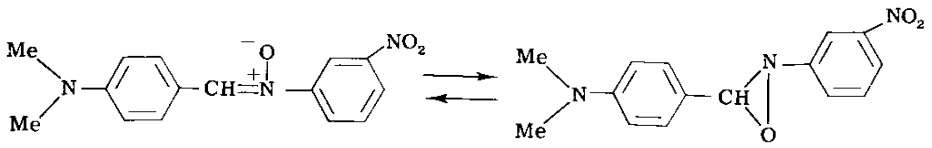
The rearrangement of 2-*tert*-butyl-3-phenyloxazirane to the isomeric nitrone is quantitative on refluxing 3 days in acetonitrile [Eq. (25)].[8]



[22] M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.* **15**, 763 (1950).

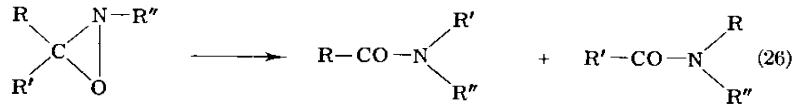
The rearrangement has been investigated kinetically. Hawthorne and Strahm found a reaction of the first order at 100°C in diethyl carbitol with $k = 5.45 \times 10^{-5}$, corresponding to a half-life of 212 min. The activation energy was 28 kcal, the activation entropy -3 ± 1 eu.[23]

The nonisolable oxazirane, which is formed by the irradiation of the diarylnitrone **31**, reverts to the nitrone even at room temperature.[17]

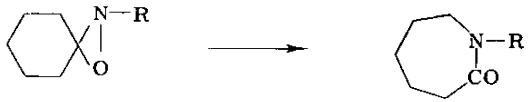


(31)

b. The Thermal Isomerization of Oxaziranes to Acid Amides. Under pyrolytic conditions *C*-alkyl oxaziranes are isomerized to acid amides. Both the isomeric acid amides which are to be expected [Eq. (26)] have in some instances been obtained (Table II). In other cases only one of the amides is produced. With oxaziranes derived from cyclic ketones, the isomerization occurs with ring expansion to an *N*-substituted lactam [Eq. (27)]. Table II gives details of the conditions used and the yields of acid amides.



(26)



(27)

Oxaziranes which carry an aryl group on nitrogen occupy a special position. Sometimes, they rearrange even at room temperature, so they cannot easily be isolated.[17] For preparative purposes, rearrangement in hot xylene is suitable.[10] For the rearrangements of *N*-alkyl-oxaziranes, boiling tetralin (207°C) is necessary.[10] The high reaction temperatures of 300°C used by Emmons[8] were selected in order to allow reaction to occur in the gas phase and to differentiate them from the liquid-phase decompositions dealt with in the following section.

[23] M. F. Hawthorne and R. D. Strahm, *J. Org. Chem.* **22**, 1263 (1957).

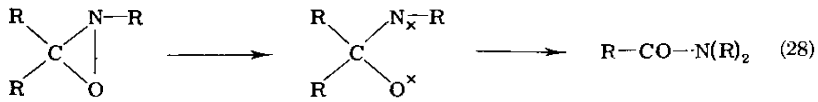
TABLE II

THERMAL ISOMERIZATION OF OXAZIRANES TO AMIDES[a]

Oxazirane	Temperature	Amide	Yield (%)	Ref.
2-Cyclohexyl-3-*n*-propyl-	>200°C	*N*-Cyclohexyl-butyramide	37	10
		N-Cyclohexyl-*N*-*n*-propyl-formamide	43	10
2-Phenyl-3,3-pentamethylene-	Boiling xylene	*N*-Phenyl-caprolactam	77	10
2-Cyclohexyl-3,3-pentamethylene-	Boiling tetralin	*N*-Cyclohexyl-caprolactam	85	10
2-*t*-Butyl-3-isopropyl-	250°C	*N*-*t*-Butyl-isobutyramide	63	8
2-*n*-Propyl-3-methyl-3-isobutyl-	300°C	*N*-Isobutyl-*N*-*n*-propyl-acetamide	24	8
		N-Methyl-*N*-*n*-propyl-isovaleramide	43	8

[a] Corresponds to Eqs. (26) and (27).

For the reaction in the gas phase, Emmons[8] proposes a homolytic O—N fission and (possibly simultaneous) alkyl shift [Eq. (28)]. The



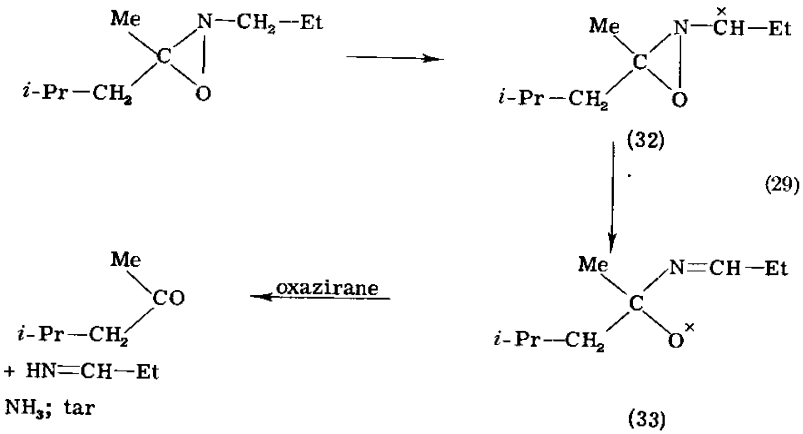
(28)

relative tendency of H, methyl, isopropyl, and isobutyl to shift does not conform to any simple law.

c. The Liquid-Phase Decomposition of Oxaziranes. Below 200°C, decomposition of oxaziranes occurs in the liquid phase. This is

different both in the type of the reaction product and also in the reaction mechanism to the pyrolytic acid amide formation.

If 2-*n*-propyl-3-methyl-3-isobutyloxazirane is allowed to boil under nitrogen, the boiling point is lowered to 128°C from the initial 168°C within 2 hr. Methyl isobutyl ketone (0.92 mole), ammonia (0.32 mole), and a little amide (0.04 mole) are formed [Eq. (29)].[8]



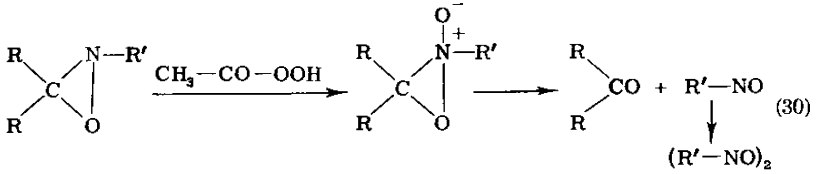
The composition of the products is reminiscent of the decomposition of the trialkyl-oxaziranes by ferrous salts. Here also the nitrogen atom is dealkylated and the carbon atom of the oxazirane ring is found as a ketone group.

The mechanism proposed by Emmons[8] thus corresponds in part to the decomposition of the trialkyl-oxaziranes by ferrous salts. By radical attack on the *N*-alkyl group of the oxazirane, the radical **32** is formed which rearranges with ring opening to **33**. Radical **33** propagates the chain by attack on a further molecule of oxazirane. It takes up an H-atom and is decomposed to ketone and ammonia. The aldehyde produced from the *N*-alkyl group is converted to tar.

The reaction described here is probably responsible for the slow decomposition of many oxaziranes at room temperature. 2-*tert*-Alkyl-oxaziranes are stable at room temperature for unlimited periods; radical attack on the α-C-atom of the *N*-alkyl group is not possible. By contrast, oxaziranes containing a C—H group which is alpha to the N-atom are unstable at room temperature: on keeping they are largely decomposed within a few weeks.

6. *Oxidative Conversion of Oxaziranes into Nitroso Compounds*

Oxaziranes are rapidly decomposed by the further action of peracids. As shown by Emmons[24] and Krimm[25] the oxazirane is converted into a carbonyl compound and a nitroso compound dimer. The reaction can be formulated via an oxazirane *N*-oxide intermediate [Eq. (30)].



The yields of the dimeric nitroso compounds are good. Thus the aliphatic nitroso compounds which previously were difficult to obtain become readily available. A series of dimeric nitroso compounds with primary and secondary alkyl groups are given in Table III.

TABLE III
DIMERIC NITROSO COMPOUNDS FROM OXAZIRANES AND PERACIDS[a]

Alkyl group of $(RNO)_2$	Yield (%)	Ref.
Isopropyl	89	25
Benzyl	37	24
n-$C_{12}H_{25}$	37	24
n-$C_{18}H_{35}$	60	24
Cyclohexyl	94	25
n-Octyl-2	83	24
β-Phenylethyl	71	24

[a] Corresponding to Eq. (30).

Dimeric nitroso compounds with tertiary alkyl groups show more tendency toward dissociation into the monomers. For example, 2-methyl-2-nitrosopropane is so volatile in the form of the monomer that it can hardly be isolated from organic solvents. For the prepara-

[24] W. D. Emmons, *J. Am. Chem. Soc.* **79**, 6522 (1957).
[25] H. Krimm and H. Schnell (Farbenfabriken Bayer A.G.) German Patent 1,073,468 (Dec. 23, 1957).

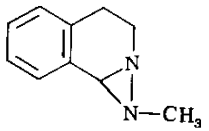
tion of 2-methyl-2-nitrosopropane, it is thus advisable first to obtain *tert*-butylhydroxylamine by acid hydrolysis of 2-*tert*-butyl-3-phenyloxazirane and to oxidize the latter with aqueous hypobromite to the nitroso compound.[24] The yield of the oxidation is 86%.

III. Diaziridines[26]

A. Preparation of Diaziridines

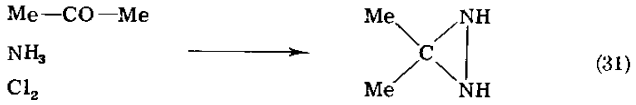
1. *Preparation of Diaziridines from Carbonyl Compounds, Amines, and Derivatives of Chloramine or Hydroxylamine*

After all the compounds which were cited in the older literature as diaziridines had been shown to be incorrectly formulated, the first authentic diaziridines appeared in the literature in 1959. Schmitz obtained *N*-methyl-1,2-diaziridino-1,2,3,4-tetrahydroisoquinoline (**34**)



(**34**)

by the reaction of 3,4-dihydroisoquinoline with *N*-chloromethylamine.[27] Abendroth and Henrich described the synthesis of 3,3-dimethyldiaziridine ("acetonisohydrazone")[28,29] by gas-phase chlorination of ammonia in the presence of acetone [Eq. (31)]. By passing ammonia and chlorine through liquid ketones, Paulsen prepared further 3,3-dialkyldiaziridines ("1,2-diazacyclopropanes").[30]



(31)

[26] For a summary see: E. Schmitz, Synthese dreigliedriger Ringe mit zwei Stickstoffatomen, Diaziridine und cyclische Diazoverbindungen, *Sitzber. Deut. Akad. Wiss. Kl. Chem. Geol. u. Biol. Berlin* No. 6 (1962).

[27] E. Schmitz, *Angew. Chem.* **71**, 127 (1959).

[28] H. J. Abendroth and G. Henrich, *Angew. Chem.* **71**, 283 (1959).

[29] H. J. Abendroth and G. Henrich (Farbenfabriken Bayer A.G.), German Patent 1,082,889 (March 17, 1958).

[30] S. R. Paulsen (Bergwerksverband G.m.b.H.), Belg. Patent 588352 (March 7, 1959).

All these syntheses form variations of the same reaction. The three-membered ring is formed from an *N*-halogenoamine with ketone–ammonia mixtures or the Schiff's base 3,4-dihydroisoquinoline. Starting from these first observations the three groups of authors were able to generalize their diaziridine syntheses quickly: in the years 1959–1962 they were extended to generally applicable reactions. In numerous variations of the syntheses, large numbers of diaziridines were prepared.

a. Ammonia and Chlorine in the Gas Phase. The diaziridine synthesis of Abendroth and Henrich[29] possesses technical interest for the preparation of hydrazine. The 3,3-dimethyldiaziridine obtained [Eq. (31)] can be quantitatively hydrolyzed to hydrazine salts. To obtain 3,3-dimethyldiaziridine, 100 moles of ammonia are allowed to react with 5 moles of acetone vapor and 2 moles of chlorine at 250 mm Hg and 85–90°C. The yield is 75%, calculated on the chlorine.

Paulsen and Huck[31] also used gas-phase chlorination of ammonia. The mixture, diluted with nitrogen, was led into excess liquid ketone. Diaziridines were obtained from methyl ethyl ketone, diethyl ketone, methyl propyl ketone, and methyl isopropyl ketone. The yields of the crude diaziridines, calculated on the chlorine, were over 90% (Table IV).

TABLE IV
3,3-Dialkyl-diaziridines (**35**)

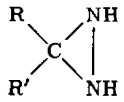
R	R′	Bp (°C)/mm	Mp (°C)	Ref.
Methyl	Methyl	106/760	40	28
Methyl	Ethyl	32/17	22	31
Ethyl	Ethyl	58/24	56	31
Methyl	*n*-Propyl	48/15	−10	31
Methyl	*i*-Propyl	67/50	55–56	31
n-Propyl	*n*-Propyl	73/11	+1	32
	3,3-Pentamethylene	Vac/subl.	103	32; 33
Methyl	Phenyl	—	41–42	32

b. Diaziridine Syntheses with Chloramine–Ammonia in Solution. For smaller laboratory preparations the method of Schmitz is suitable. *tert*-Butylhypochlorite is dropped into methanolic ammonia at −40°C[32]; after the addition of a ketone, diaziridine formation occurs

[31] S. R. Paulsen and G. Huck, *Chem. Ber.* **94**, 968 (1961).

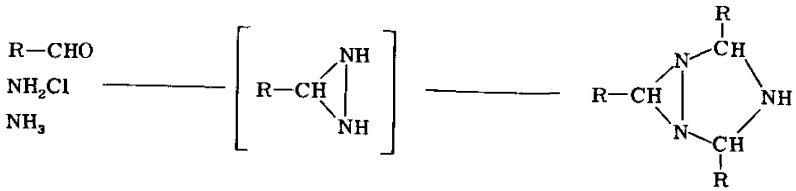
[32] E. Schmitz and R. Ohme, *Chem. Ber.* **94**, 2166 (1961).

on warming to room temperature. For example, 3,3-di-*n*-propyldiaziridine (**35**; R, R′ = C_3H_7) was prepared from 4-heptanone.



(35)

By the same method, diaziridines can be prepared from aldehydes.[34] Here the reaction does not stop at the stage of the diaziridine unsubstituted at the N-atom (**36**); further condensation of two aldehyde



(36) (37)

molecules and ring closure with ammonia occurs to give compounds of type (**37**). A few of the diaziridino-triazolidines (**37**) prepared according to this method are noted in Table V.

TABLE V

3,5,3′-TRIALKYL-DIAZIRIDINO-(1′,2′:1,2)-1,2,4-TRIAZOLIDINES (**37**)

Starting material	Yield (%)	Mp (°C)	Ref.
Acetaldehyde	46	114–115	34
Propionaldehyde	74	104–105.5	34
n-Butyraldehyde	80	84–86	34
Benzaldehyde	32	160–162	34

c. Syntheses of N-Substituted Diaziridines from Schiff's Bases. From the observation that cyclic Schiff's base 3,4-dihydroisoquinoline reacts with *N*-chloromethylamine to give a diaziridine,[27] Schmitz and

[33] H. J. Abendroth, *Angew. Chem.* **73**, 67 (1961).
[34] E. Schmitz, *Chem. Ber.* **95**, 688 (1962).

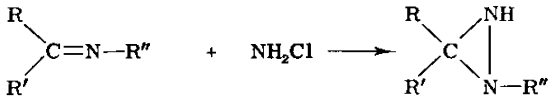
Habisch[35] investigated the action of chloramine on simple Schiff's bases. In the aliphatic series, diaziridine formation was observed in all the cases investigated. Ethereal solutions of chloramine react with Schiff's bases at room temperature within a few hours [Eq. (**32**)]. Table VI gives details of a few of the 1-alkyl-diaziridines prepared.

TABLE VI

1-ALKYL-DIAZIRIDINES FROM SCHIFF'S BASES AND CHLORAMINE[a]

Schiff's Base from Carbonyl compound	Amine	Yield (%)	Mp (°C)	Ref.
Propionaldehyde	Cyclohexylamine	55	28	35
Oenanthaldehyde	Cyclohexylamine	54	18	35
Oenanthaldehyde	*n*-Butylamine	53	16	35
Butyraldehyde	Benzylamine	26	13	35
Acetone	Cyclohexylamine	64	17	35
Acetone	Isopropylamine	40	−9	35
Cyclohexanone	Cyclohexylamine	71	36	35

[a] Corresponds to Eq. (32).



(32)

The reactions of chloramine are not generally successful with *N*-chloroalkylamines. Therefore it was surprising that the diaziridine synthesis occurred smoothly from aliphatic Schiff's bases and *N*-chloroalkylamines [Eq. (33), Table VII]. As can be seen from examples

TABLE VII

1,2,3-TRIALKYL DIAZIRIDINES FROM SCHIFF'S BASES AND *N*-CHLOROALKYLAMINES[a;20]

1-Alkyl	2-Alkyl	3-Alkyl	Bp (°C)/mm	Yield (%)
n-Butyl	*n*-Butyl	Methyl	50/1.5	64
Methyl	Cyclohexyl	Ethyl	91/11	57
n-Butyl	*n*-Butyl	*n*-Propyl	104–105/10	71
Methyl	*n*-Butyl	*n*-Hexyl	111/10	63
n-Butyl	*n*-Butyl	*n*-Hexyl	107/0.8	53

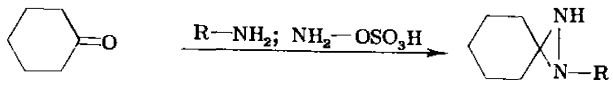
[a] Corresponds to Eq. (33).

[35] E. Schmitz and D. Habisch, *Chem. Ber.* **95**, 680 (1962); E. Schmitz, German Patent 1,107,238 (Dec. 21, 1959).

(33)

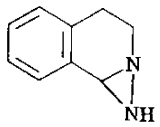
in Table VII, diaziridines with two different substituents on nitrogen can also be prepared.

d. Diaziridine Syntheses with Hydroxylamine-O-sulfonic Acid. As shown by Abendroth,[33] and by Schmitz and Ohme,[32] hydroxylamine-*O*-sulfonic acid can be used with advantage in place of chloramine. From cyclohexanone, ammonia and hydroxylamine-*O*-sulfonic acid 3,3-pentamethylenediaziridine is formed [Eq. (34), R = H] in yields



(34)

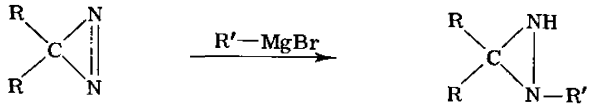
up to 80%. If *n*-propylamine[33] or methylamine[36] is used in place of ammonia, the corresponding diaziridine substituted in the 1-position is obtained. From 3,4-dihydroisoquinoline the diaziridine **38** was synthesized.[37]



(38)

2. *Diaziridine Syntheses from Diazirines and Grignard Compounds*

A further synthesis of 1-alkyl-diaziridines is the addition of Grignard compounds to the NN double bond of diazirines [Eq. (35)]. The



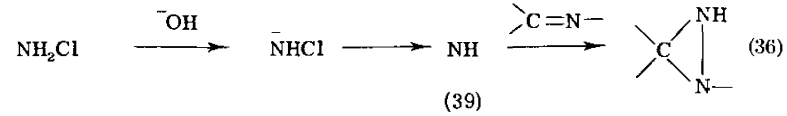
(35)

diaziridines are often produced in excellent yields[32]; details are given in Section IV,C.

[36] E. Schmitz, R. Ohme, and R. D. Schmidt, *Chem. Ber.* **95**, 2714 (1962).
[37] E. Schmitz and R. Ohme, *Chem. Ber.* **95**, 2012 (1962).

3. *Mechanism of Diaziridine Formation*

A final statement on the mechanism of the diaziridine formation cannot yet be made. The obvious formulation [Eq. (36)] as a reaction of the CN double bond with the imen **39** (with an electron sextet) is almost certainly excluded. The formation of **39** as an intermediate has been proposed for the Raschig hydrazine synthesis, but has been disputed.[38] The following facts are against a diaziridine formation corresponding to Eq. (36):

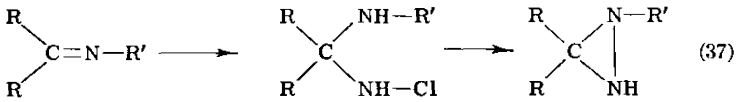


(36)

(39)

In contrast to the Raschig hydrazine synthesis, diaziridine formation occurs in solvents of low polarity such as ether and in the absence of strong bases. An ionization of chloramine and the formation of **39** is thus unlikely.

The rate of the diaziridine formation shows that the chloramine is attacked by the Schiff's base. Although ethereal chloramine solutions are only decomposed after weeks of standing, in the presence of a Schiff's base the chloramine is consumed after a few hours. The Schiff's base therefore does not enter into the reaction merely after the decomposition of the chloramine as it would have to do if formula **39** was an intermediate. Probably the chloramine adds onto the Schiff's base [Eq. (37)] and ring closure of the geminal addition product occurs.[39]



(37)

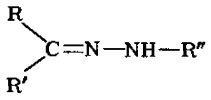
+ NH_2Cl

B. Proof of Structure and Properties of Diaziridines

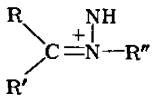
Diaziridines are decomposed on acid hydrolysis into 1 mole of carbonyl compound and 1 mole of a hydrazine. This shows the presence

[38] For a review see: J. Fischer and J. Jander, *Z. anorg. u. allgem. Chem.* **313**, 14 (1961).
[39] E. Schmitz, Lecture at the Butlerow Symposium, Leningrad, Dec. 15, 1961. *J. Allunions-Chem. Ges., D. I. Mendelejew*, p. 343 (1962).

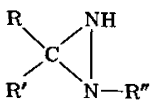
of an NN-bond. The structural evidence found by the discoverers of the diaziridines had to be reconciled with formulas **2**, **40**, or **41**, which



(40)



(41)



(2)

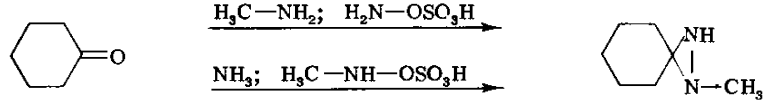
could all obviously explain the hydrolysis to a carbonyl compound and a hydrazine derivative.

The hydrazone structure **40** can be eliminated at once: many examples of this class of compounds are known and their properties are completely different from the diaziridines. For example, 3,3-dimethyldiaziridine has a heat of combustion of about 35 kcal higher than the isomeric acetone hydrazone.[28] Further pairs of isomers of diaziridines and hydrazones are known.[35] The spectrum eliminates both the hydrazone structure and the betaine structure **41**. The diaziridines do not absorb in the UV range. In the infrared spectrum, absorption is completely absent in the double-bond region.[28,31,35] The NMR spectrum of 3,3-dimethyldiaziridine is in agreement with a formulation that has two equivalent *N*-protons.[28]

After the elimination of structures **40** and **41**, structure **2** with the CNN three-membered ring remains. This structure gains weight by various parallels to the oxaziranes. The CN double bond of the Schiff's base disappears if one either treats it with peracid to give an oxazirane or with chloramine to give a diaziridine. Cyclohexanone gives with methylhydroxylamine-*O*-sulfonic acid an oxazirane (Section II,A,3); in the presence of ammonia the same reagents give a diaziridine **42**. Both these classes of compounds are strong oxidizing agents which quantitatively convert iodide to iodine. A band found by Krimm[10] in the infrared spectrum of the oxaziranes at ca. 1400 cm^{-1} finds its parallel with the diaziridines in a medium-to-strong band between the C—H vibrations at 1380 and 1460 cm^{-1}.

A simple chemical proof of structure of the diaziridines is given by the synthesis of the same diaziridine **42** from cyclohexanone either using methylamine and hydroxylamine-*O*-sulfonic acid or using ammonia and methylhydroxylamine-*O*-sulfonic acid.[36]

Further evidence for the three-ring structure is given by the mutual interconversions of diaziridines and diazirines (Section IV).

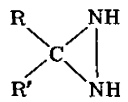


(42)

All the diaziridines described in the preceding sections can be distilled; however, lengthy heating above 100°C should be avoided. An explosion on working with 3,3-dimethyldiaziridine has been reported.[40] Probably, however, 3,3-dimethyldiazirine which had been formed by dehydrogenation was responsible for the explosion.

The physical properties of the diaziridines depend on the degree of *N*-substitution. Compounds (**35**) which are unsubstituted on both nitrogen atoms are well crystallized. The diaziridines which are mono-*N*-alkylated (**43**) also crystallize without exception, but have melting points at approximately room temperature or below (Table VI). In contrast to the diaziridines of type (**35**) the mono-*N*-substituted analogs are insoluble in water. However, low molecular weight compounds such as 2-ethyl-3-methyldiaziridine are exceptional in being easily soluble in water. In organic solvents including petroleum ether, the 1-alkyl-diaziridines (**43**) are easily soluble. They can only be recrystallized at low temperatures from ether or pentane.

The diaziridines which are di-*N*-substituted (**44**) do not crystallize. They are miscible with all organic solvents.



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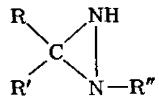
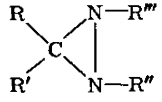


(43)



(44)

Diaziridines are weak bases.[35] They can be extracted from organic solvents with aqueous mineral acids. With increasing number and chain length of alkyl substituents the solubility in aqueous mineral acids decreases. 1-Methyl-2-*n*-butyl-3-hexyldiaziridine is soluble only in concentrated hydrochloric acid. Stable oxalates can in some cases be prepared from 1-alkyl-diaziridines (**43**).[35] The salts are stable indefinitely and by the action of alkali the diaziridines can be recovered. Diaziridines dialkylated on nitrogen (**44**) are hardly capable of salt

[40] H. J. Abendroth, *Angew. Chem.* **71**, 340 (1959).

formation. With complex acids such as hydroferrocyanic acid they form crystalline adducts which can serve for the purification of the diaziridines.[20]

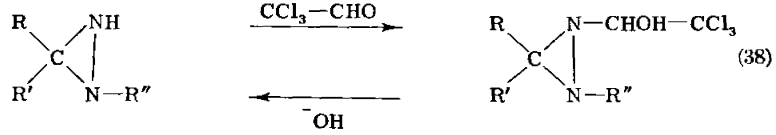
C. Reactions of Diaziridines

The diaziridines are somewhat more stable than the oxaziranes. The three-membered ring of the oxaziranes is decomposed in all of its reactions, but with the diaziridines substitution on the nitrogen atoms can be effected and reactions involving fission and expansion of the ring to a five-membered ring are possible.

1. *Reactions of the Diaziridines with Retention of the Three-Membered Ring*

A few reagents react with the N—H groups of the diaziridines. It is easy to decide whether the resulting compounds still contain a true diaziridine ring by testing for the characteristic property of such rings to liberate from iodide solution two equivalents of iodine.

All diaziridines which contain at least one NH-group give, with chloral, well crystallized addition products in molar ratio 1:1.[41] The adducts liberate two equivalents of iodine and thus retain the CNN three-membered ring [Eq. (38)]. By treatment with alkali the chloro-



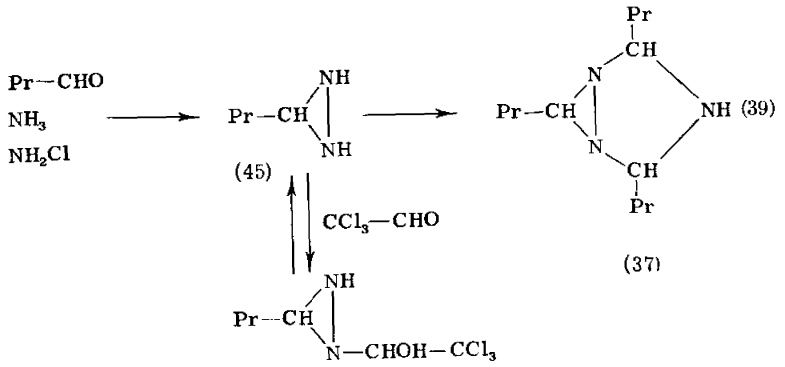
(38)

form fission reaction of chloral takes place with liberation of diaziridine. The chloral adducts therefore serve both to characterize and to purify diaziridines.

With aldehydes some diaziridines condense under the conditions of preparation. The formation of a fused triazolidine ring occurs regularly if aldehydes are treated with ammonia and chloramine to give diaziridines[34] [Eq. (39)]. If, however, chloral is added previously to the reaction mixture, the 3-alkyl-diaziridines (**45**) are caught as their chloral adducts. By the alkali fission of these chloral adducts, 3-alkyl-diaziridines, e.g. (**45**), can be prepared.[42]

Acylation yields products retaining the three-membered ring only if the diaziridine is derived from an aldehyde. 3,3-Dialkyl-diaziridines

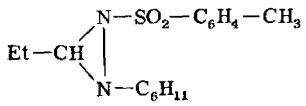
[41] E. Schmitz and R. Ohme, *Chem. Ber.* **95**, 795 (1962).
[42] E. Schmitz and D. Habisch, *Rev. chim.* (*Bucharest*), in press.



(i.e., derived from ketones) react without exception with fission of the three-membered ring.

From 1-cyclohexyl-3-ethyldiaziridine, crystalline derivatives have been prepared with *p*-toluenesulfonyl chloride and with 3,5-dinitrobenzoyl chloride, e.g., **46**.[42] The quantitative liberation of iodine from acid iodide solution characterizes these compounds as true diaziridines.

For the characterization of 1,3-dialkyl-diaziridines, derivatives can be prepared with phenyl isocyanate. The reaction products (**47**) are



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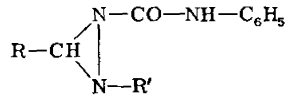


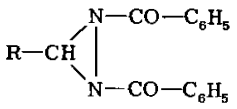
(47)

isomers of semicarbazones containing a three-membered ring. The liberation of iodine is quantitative in all cases (Table VIII).[42]

TABLE VIII
1-Alkyl-2-anilinoformyl-3-alkyl-diaziridines ("Isosemicarbazones") (**47**)

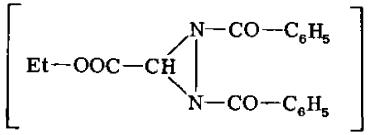
1-Alkyl	3-Alkyl	Yield (%)	Iodine liberated (%)	Ref.
Cyclohexyl	Ethyl	85	99.5	42
Ethyl	Methyl	86	100	41
Benzyl	*n*-Propyl	67	98	42
Cyclohexyl	*n*-Propyl	90	97.5	41

3-Methyldiaziridine and 3-*n*-propyldiaziridine (**45**) give with benzoyl chloride the dibenzoyl compounds **48** and **49**.[42] Both compounds are shown to be true diaziridines by oxidizing iodide. This discovery was of special interest: the sole compounds retained in recent literature[3,4] of those formerly formulated as diaziridines were supposedly 1,2-diacyl-diaziridines, e.g. **50** [compare Section I, Eq. (1)].



(48): R = Me

(49): R = Pr



(50)

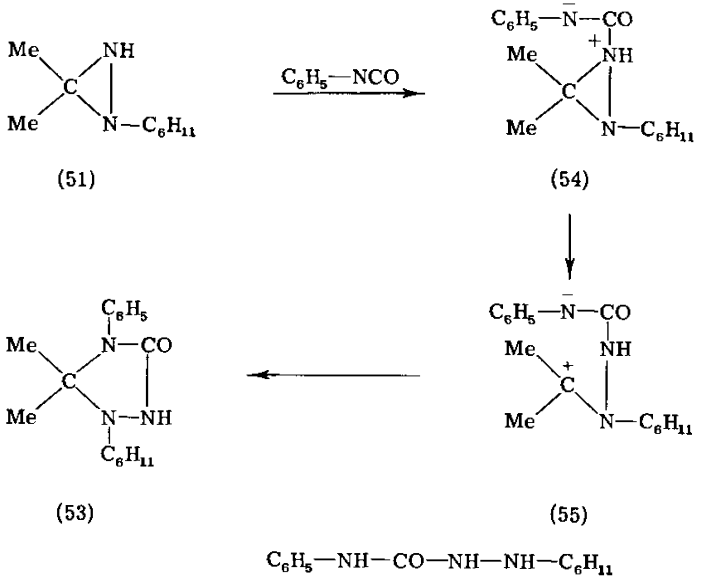
These compounds, however, show no oxidizing power. Their diaziridine structure is thus erroneous.[42]

2. *Reactions of Diaziridines with Ring Expansion*

1,3,3-Trialkyl-diaziridines (e.g. **51**) react with phenyl isocyanate with the same ease as the 1,3-dialkyl analogs. However, the compounds which result from the components in ratio 1:1 are not oxidizing agents and thus are not diaziridines.[42]

The compound prepared from 1-cyclohexyl-3,3-dimethyldiaziridine (**51**) and phenyl isocyanate gave by acid hydrolysis 1-cyclohexyl-4-phenyl semicarbazide (**52**). Assumption of a ring expansion during the formation of the derivative gives structure **53**. The interpretation of the course of this reaction must explain the influence of the substituents on the C-3 atom. One alkyl group at C-3 leads to the isolation of a product with an intact three-membered ring; double alkyl substitution at C-3 always causes ring expansion. This increased reactivity as a result of increased alkyl substitution indicates an S_N1 ionization for the opening of the three-membered ring. This ionization is initiated by the appearance of a positive charge on the ring nitrogen atom in the course of the acylation (**54**). The ionic ring opening (**54** → **55**) is followed by stabilization of the molecule by a new ring closure to **53**.

The same ring expansion occurs on the reaction of 3,3-di-*n*-propyldiaziridine with two molecules of phenyl isocyanate [Eq. (40)].[42]

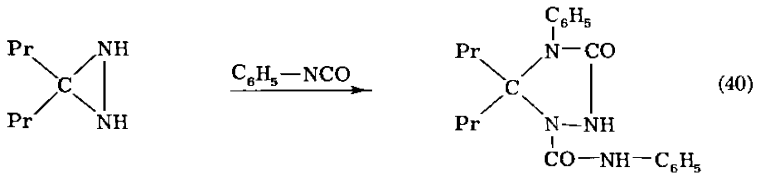


(51) (54) (53) (55)

C_6H_5—NH—CO—NH—NH—C_6H_{11}

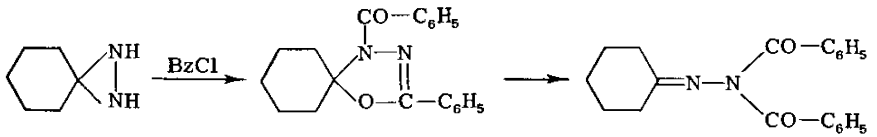
(52)

In the benzoylation of 3,3-pentamethylenediaziridine, an oxygen-



(40)

containing five-membered ring is formed by ring expansion (**56** mp 98°C). Compound **56** is very unstable as it is a cyclic iminoether.



(56)

On mild heating of its ethanolic solution, rearrangement occurs with the shift of a benzoyl group. The structure of the cyclohexanone

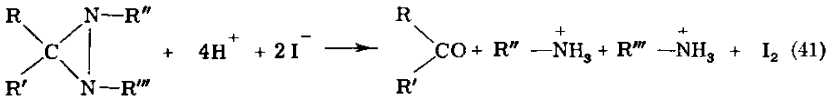
dibenzoylhydrazone (mp 120°C) follows from an independent synthesis.[42]

3. *Ring Fission Reactions of Diaziridines*

In their thermal stability the diaziridines approximate to the oxaziranes. As with most oxaziranes, they are stable at 100°C for short periods; they are decomposed by heating at 200°C: 1,2-di-*n*-butyl-3-*n*-propyldiaziridine thus eliminates butylamine. The thermal decomposition has not yet been investigated in detail. Similarly no information is available on the reaction of radical reagents on diaziridines.

Diaziridines are stable toward alkalies. Aqueous alkali attacks pentamethylenediaziridine on heating not more quickly than does pure water. Further investigation has not yet been undertaken. However, reductive fission and hydrolytic fission in acid media have been studied in detail.

a. Reductive Fission of Diaziridines. As already mentioned, diaziridines liberate two equivalents of iodine from acid iodide solution quantitatively[28,31,35] [Eq. (41)]. Titration with thiosulfate allows de-

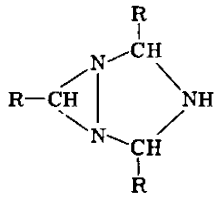


(41)

termination of the diaziridine. In the titrated aliquots, the four equivalents of acid used can be measured by back titration with normal alkali providing the basicity of the amine produced is sufficient.

The rate of iodine formation depends on the degree of *N*-substitution. Compounds which are unsubstituted on both the *N*-atoms (**35**) and those with a single *N*-substituent (**43**) liberate instantly the calculated quantity of iodine in the cold. However, the 1,2-disubstituted diaziridines (**44**) need brief heating with the acid iodine solution; they then give 95–100% of the calculated iodine.[20] This effect of substitution is so well defined that it can be used for a proof of constitution. The diaziridino-triazolidines (**37**) prepared from aldehydes, ammonia, and chloramine give complete iodine liberation only on heating. Thus the structure **57** which is isomeric with **37** can be eliminated.[34]

Although compound **38** liberates the calculated amount of iodine,[37] the completely alkylated compound **34** only gives traces of iodine. The



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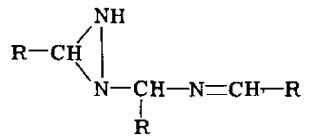

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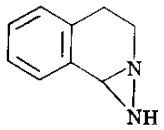
very rapid hydrolysis characteristic of *C*-arylated diaziridines can compete successfully in the case of compound **34** with the liberation



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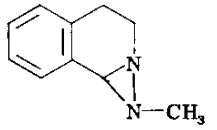
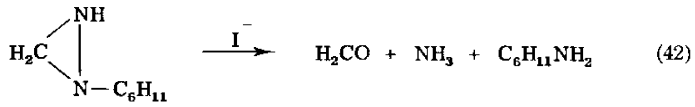


(34)

of iodine which is here slowed down by alkyl substitution.

The amines which are formed by the iodide reduction [Eq. (41)] can be isolated and used in the proof of structure of the diaziridines. For example, ammonia and cyclohexylamine were obtained from 1-cyclohexyldiaziridine [Eq. (42)][41]; cyclohexylamine and phenylurea were obtained from the acylated diaziridine **58** [Eq. (43)].[35]



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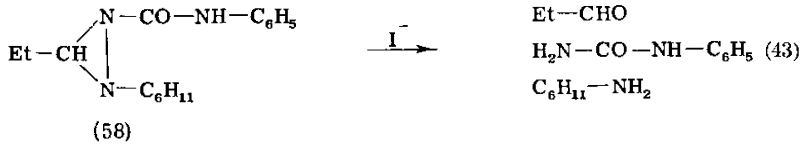
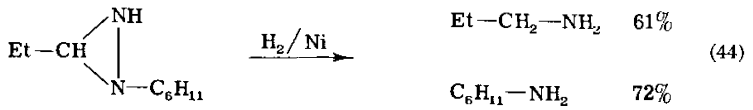


(58)

(43)

The catalytic hydrogenation of diaziridines also begins with a reductive opening of the NN-bond. However, hydrogenation usually stops only after the uptake of 2 moles of hydrogen. The carbonyl compound corresponding to the diaziridine reacts under the reducing conditions with one of the amines. For example, the hydrogenation of 1-cyclohexyl-3-ethyldiaziridine over Raney nickel gives *n*-propyl-

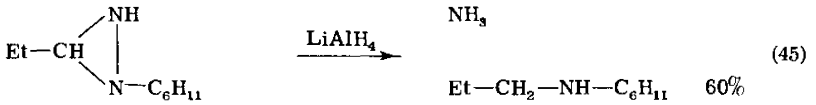
amine and cyclohexylamine [Eq. (44)].[35] Under the same conditions, tetrahydroisoquinoline and methylamine are formed from the diaziridino-isoquinoline derivative **34**.[43]



(44)

(59)

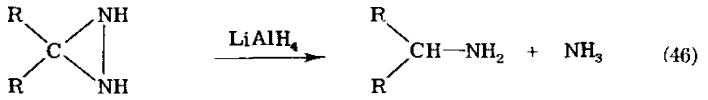
Lithium aluminum hydride only reacts with diaziridines if at least one of the N-atoms is unsubstituted. Here again an NN-fission occurs. However, the reduction can give products other than those formed from catalytic hydrogenation. Thus the reduction of compound **59** with lithium aluminum hydride gave as the main product *n*-propylcyclohexylamine with ammonia [Eq. (45)].[35] The reduction of 3,3-



(45)

(59)

diethyldiaziridine by lithium aluminum hydride to 3-aminopentane and ammonia was used by Paulsen and Huck for structural proof [Eq. (46)].[31]



(46)

1,2-Dialkyl-diaziridines are not attacked by lithium aluminum hydride: 1,2-di-*n*-butyl-3-*n*-propyldiaziridine (**60**) was recovered in 80% yield after treatment with lithium aluminum hydride in boiling ether. A preparative separation of **34** and 3,4-dihydroisoquinoline is possible by treating the mixture with lithium aluminum hydride when compound **34** is unattacked.[43]

Finally, the oxidative action of diaziridines toward hydrogen sulfide

[43] E. Schmitz, *Chem. Ber.* **95**, 676 (1962).

and hydrogen chloride has been reported.[31] The action of dry hydrogen chloride on 3-methyl-3-ethyldiaziridine gives, by unknown mechanism, ammonium chloride, 2-chlorobutane, and nitrogen. Hydrogen sulfide reacts slowly with diaziridines to give ketones, sulfur, and hydrazine.

b. Hydrolytic Fission of Diaziridines. The hydrolytic fission of diaziridines to carbonyl compounds and hydrazine derivatives is a general reaction. The hydrolysis of 3,3-dimethyldiaziridine has been proposed for the technical production of hydrazine.[29] The preparation of hydrazine by way of a diaziridine has several advantages compared to the Raschig syntheses. For example, no sodium hydroxide is necessary and the reaction products are not obtained as dilute aqueous solutions.

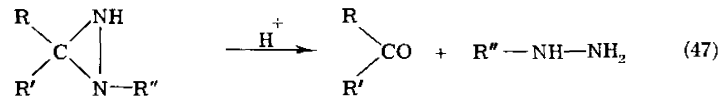
More important preparatively is the hydrolysis of 1-alkyl-diaziridines to alkyl hydrazines [Eq. (47)].[35] A number of the alkyl hydrazines thus prepared are shown in Table IX. The synthesis of alkyl

TABLE IX

ALKYL HYDRAZINES BY HYDROLYSIS OF 1-ALKYL-DIAZIRIDINES

Diaziridine	Alkyl hydrazine	Yield (%)	Ref.
1-Cyclohexyl-3-ethyl-	Cyclohexylhydrazine	88	35
1-*n*-Butyl-3-*n*-hexyl-	*n*-Butylhydrazine	77	35
1-Benzyl-3-*n*-propyl	Benzylhydrazine	87	35
1-Ethyl-3-methyl-	Ethylhydrazine	48	35
1-Isopropyl-3,3-dimethyl-	Isopropylhydrazine	83	35
1-*n*-Propyl-3,3-pentamethylene-	*n*-Propylhydrazine	88	44

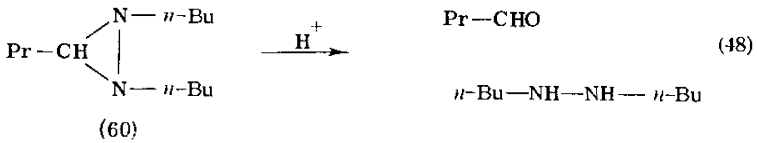
hydrazines from diaziridines is preferable to the direct reaction of amines with chloramine or hydroxylamine-*O*-sulfonic acid because the yields calculated on the amine are higher.



(47)

The hydrolysis of 1,2-dialkyl-diaziridines to *N,N'*-dialkyl hydrazines is equally possible. Di-*n*-butylhydrazine is produced from 1,2-di-*n*-butyl-3-*n*-propyldiaziridine (**60**) [Eq. (48)].[20]

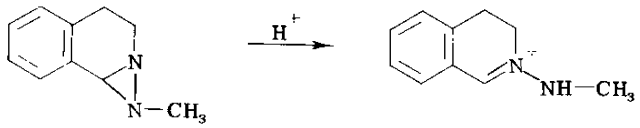
[41] E. Schmitz and R. Ohme, *Angew. Chem.* **73**, 220 (1961).



(48)

(60)

The hydrolysis of the diaziridine **34** to the cyclic hydrazonium salt **61** [Eq. (49)][43] occurs quantitatively. Hydrolysis of the diaziridinotriazolidine (**37**) gives 3 moles of aldehyde and 1 mole each of hydrazine and ammonia [Eq. (50)].[34]



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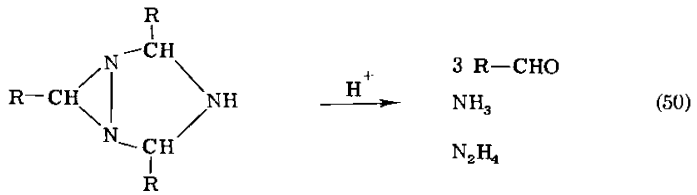
(34) (61)



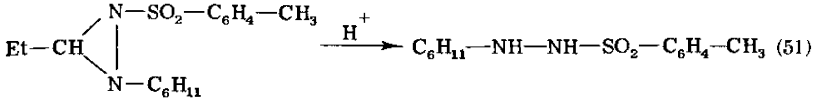
(50)

(37)

The hydrolysis of 1-alkyl-2-acyldiaziridines to *N*-alkyl-*N'*-acylhydrazines possesses preparative interest. For example, *N*-cyclohexyl-*N'*-toluenesulfonylhydrazine [Eq. (51), yield 67%] and 1-cyclohexyl-4-phenylsemicarbazide [Eq. (52), yield 73%] can be prepared by hydrolysis of the substituted diaziridines **46** and **62**.[42]

The acid hydrolysis of diaziridines has been investigated kinetically.[45] The reaction is first order and shows a relatively high temperature coefficient. Thus one finds a relatively high activation enthalpy (23–28 kcal) and a positive activation entropy (2–6 eu). The influence of substitution on nitrogen is small. The velocity of the diaziridine hydrolysis depends only in the weakly acid region on the acid concentration. Between pH 7 and 3 the *k*-values rise by nearly 10^3. For the

[45] Cs. Szántay and E. Schmitz, *Chem. Ber.* **95**, 1759 (1962).



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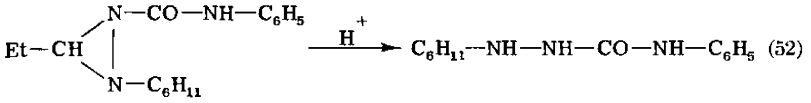


(52)

(62)

transition from pH 3 to 70% sulfuric acid, the *k*-values are further increased merely by the factor 4. The hydrolysis therefore must be preceded by a protonation which is already almost complete at pH 3.

The substitution on the C-atom is by contrast of great effect on the rate of hydrolysis. Table X gives the half-life values for the fission

TABLE X

HALF-LIVES OF THE HYDROLYSIS OF SOME DIAZIRIDINES[a]

Diaziridine	Half-life[b] (min)
1,2-Diaziridino-1,2,3,4-tetrahydroisoquinoline (**38**)	2[c]
1-Cyclohexyl-3,3-dimethyldiaziridine	19.8
1-Cyclohexyl-3-methyldiaziridine	1630
1-Cyclohexyldiaziridine	35000[c]

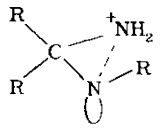
[a] Followed iodometrically.[45]
[b] In 2 *N* H_2SO_4 at 35°C.
[c] Extrapolated.

of a few diaziridines in 2 *N* sulfuric acid at 35°C. The values show the increase of the reaction velocity with increasing alkyl substitution typical for S_N1 processes. The rate-determining step of the hydrolysis is, therefore, an ionic opening of the diaziridinium ion (**63**) [Eq. (53)].

(53)

(63)

However, diaziridines are many times more stable to hydrolysis than the open-chain compounds containing the group N—C—N. Whereas, for example, methylenediamines in general are unstable toward acid, the cyclic methylenediamine 1-cyclohexyldiaziridine is only half hydrolyzed after 24 days (Table X). An explanation of the resistance of hydrolysis of the diaziridines has been proposed by Szántay and Schmitz. Facilitation of the ring opening [Eq. (53)] by the lone electron pair on the noncharged nitrogen atom is difficult.[45] This lone electron pair is both deactivated by the positively charged neighboring nitrogen atom and subject to unfavorable stereoelectronic factors. Structure **64** shows the large angle between the two orbitals which must interact. In **64** the plane formed by the R—C—R group



(64)

lies in the plane of the drawing, and the three-membered ring in a plane at right angles to this. In the course of the ionization of the carbon atom, an empty orbital is formed perpendicular to the plane of the drawing. The orbital of the spare electron pair on the uncharged nitrogen is at an angle of over 60° to the empty orbital, thus overlap of the two orbitals is hindered.

Similar reasons may explain the considerable stability of oxaziranes toward acids.

IV. Diazirines

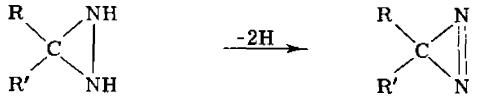
In the discussion on the structure of the aliphatic diazo compounds, the question of the existence of isomeric diazo compounds with three-membered rings was never considered. It was therefore a surprise when the cyclic diazo compounds, i.e. the diazirines, became known: their preparation was published independently by Paulsen[46] and by Schmitz and Ohme.[47]

A. Preparation of Diazirines

3,3-Dialkyl-diaziridines (**35**) possess a considerable reducing power: they are dehydrogenated by yellow mercuric oxide or alkaline per-

[46] S. R. Paulsen, *Angew. Chem.* **72**, 781 (1960).
[47] E. Schmitz and R. Ohme, *Angew. Chem.* **73**, 115 (1961).

manganate solution[46] and solutions of 3,3-dialkyl-diaziridines form a silver mirror on shaking with silver oxide within a few seconds[32,47]; two hydrogen atoms are eliminated according to Eq. (54). The prod-



(35) (65) (54)

ucts of dehydrogenation can be isolated in good yields. Their reactions show that they are isomeric with the aliphatic diazo compounds and are, indeed, the diazirines **65**. The yields and boiling points of some diazirines are shown in Table XI.

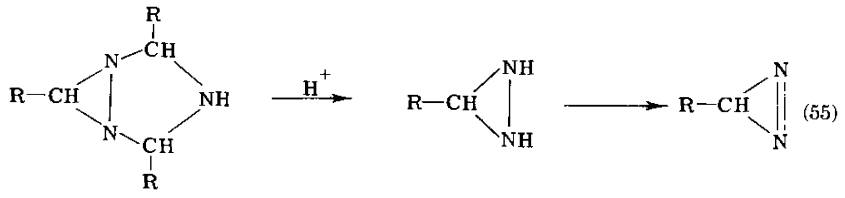
TABLE XI
3,3-Dialkyl-diazirines[a]

R	R′	Yield (%)	Bp (°C)/mm	Ref.
Methyl	Methyl	70	21/760	32
Methyl	Ethyl	—	47/760	46
Ethyl	Ethyl	—	80–81/760	46
n-Propyl	*n*-Propyl	81	24–25/11	32
Methyl	Phenyl	76	58–59/11 (mp. −5°C)	32
3,3-Pentamethylene		67	33/30	47, 32

[a] Prepared according to Eq. (54).

The diazirines can be prepared from the simplest starting materials. Their production needs only ketone, ammonia, chlorine, and an oxidizing agent. Attempts to prepare 3-alkyl-diazirines from aldehydes under the same conditions were at first met with difficulties. 3-Alkyl-diaziridines (**36**) could only be prepared in the form of the diaziridino-triazolidines (**37**).[34] In these compounds the N—H groups that need to be dehydrogenated were blocked. However, the N—C—N group in the three-membered ring is more stable toward hydrolysis than the same group in a chain or in a larger ring, enabling fission of the five-membered ring by partial hydrolysis without attacking the three-membered ring. The preparation of the 3-alkyl-diazirines (**66**) succeeded when the hydrolysis of the diaziridino-triazolidines (**37**) was effected in the presence of dichromate: the liberated 3-alkyl-diaziridine

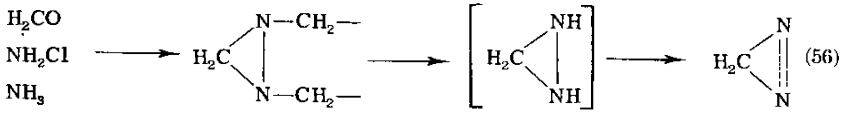
(36) was at once dehydrogenated to the 3-alkyl-diazirine (66) [Eq. (55)].[41,48]



(37) (36) (66) (55)

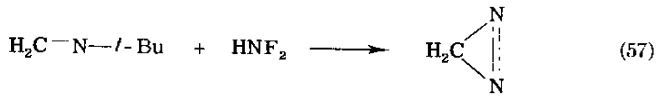
3-*n*-Propyldiazirine and 3-ethyldiazirine are low boiling liquids which were not prepared in the pure form because of their explosive character. 3-Methyldiazirine is gaseous (bp −6°C).

For the preparation of the parent substance, cyclic diazomethane (67), formaldehyde, chloramine, and ammonia were reacted. Diaziridine formation was successful in about 20% yield; the diaziridine condensed with further formaldehyde to high molecular weight products: the diaziridine detected by its oxidizing power was nonvolatile. Oxidation with dichromate in dilute sulfuric acid led to gaseous diazirine (67) [Eq. (56)].[41,48] It was only investigated in solution.



(67) (56)

Graham[49] recently reported a second synthesis of diazirine [Eq. (57)]. The yield reached 62%.



(67) (57)

[48] E. Schmitz and R. Ohme, *Tetrahedron Letters* No. 17, p. 612 (1961).
[49] W. H. Graham, *J. Am. Chem. Soc.* 84, 1063 (1962).

B. Properties of Diazirines

The diazirines are of special interest because of their isomerism with the aliphatic diazo compounds. The diazirines show considerable differences in their properties from the aliphatic diazo compounds, except in their explosive nature. The compounds 3-methyl-3-ethyldiazirine and 3,3-diethyldiazirine prepared by Paulsen[46] detonated on shock and on heating. Small quantities of 3,3-pentamethylenediazirine (68) can be distilled at normal pressures (bp 109°C).[32] On overheating, explosion followed. 3-*n*-Propyldiazirine exploded on attempts to distil it a little above room temperature.[41] 3-Methyldiazirine is stable as a gas, but on attempting to condense ca. 100 mg for vapor pressure measurements, it detonated with complete destruction of the apparatus.[41] Diazirine (67) decomposed at once when a sample which had been condensed in dry ice was taken out of the cold trap.[41] Work with the lower molecular weight diazirines in condensed phases should therefore be avoided.

In their thermal stability the diazirines appear to be superior to the isomeric aliphatic diazo compounds. Paulsen reports for his diazirines decomposition temperatures of 220–230°C.[46] 3,3-Pentamethylenediazirine (68),[32] which was led in a stream of nitrogen through a spiral heated with boiling tetralin (bp 207°C), still contained appreciable amounts of unaltered starting material. In high boiling point solvents, thermal decomposition can be controlled. Decomposition with nitrogen evolution occurs on heating 3,3-pentamethylenediazirine (68) in nitrobenzene at ca. 165°C.

Molecular weight determinations have been carried out with methylethyl-, diethyl-, di-*n*-propyl-, pentamethylene-, and methylphenyldiazirine. They gave monomeric molecular weights. The three last-named compounds gave the calculated C, H, and N values by the usual procedure of microanalysis.

In contrast to the aliphatic diazo compounds, which are invariably colored, all the diazirines so far prepared are colorless. The UV absorption of diazirines corresponds approximately to that of the aliphatic azo compounds.[48] Diazirine shows in methanol an absorption maximum at 321 mμ. The IR spectrum of the diazirines shows a band at ca. 1580 cm^{-1}.

The diazirines are insoluble in water. They are completely miscible with all organic solvents. The only crystalline compound so far known, 3-methyl-3-phenyldiazirine, can be recrystallized from ether.

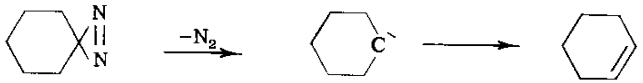
The diazirines have no basic character, they are not attacked even by strong mineral acids. 3,3-Pentamethylenediazirine (**68**) could be recovered almost unchanged after the action of methanolic 3 *N* hydrochloric acid for 1 hr.[32] Strong alkalies are also without effect: diazirine (**67**) is unchanged by passing through concentrated sodium hydroxide solution after preparation to eliminate carbon dioxide which is formed simultaneously.[41]

The properties of the diazirines and the analytical results showed that a new class of isomeric diazo compounds had been discovered. The three-membered ring structure (**65**), which is made probable by the synthetic methods, is confirmed by the reactions of the diazirines.

C. Reactions of Diazirines

The cyclic diazo compounds (diazirines **65**) are very unreactive compounds. Specially noticeable is the absence of the reactivity toward electrophilic reagents which is characteristic of the linear isomers. Acids or aldehydes which react smoothly with the aliphatic diazo compounds are without action on the cyclic diazo compounds. Iodine does not attack the cyclic diazo compounds.

Thermal decomposition gives olefins, probably by rearrangement of intermediate carbenes. For example, the decomposition of 3,3-pentamethylenediazirine (**68**) in nitrobenzene above 160°C gives cyclohexene [Eq. (58)].[32] The yield as determined by bromine titration



(58)

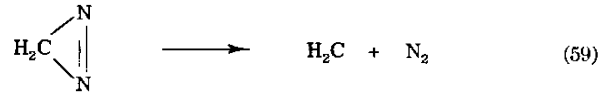
(68)

was 80%. The thermal decomposition of 3,3-di-*n*-propyldiazirine gave olefins (ca. 90%). Olefin formation is characteristic of carbenes with α-CH groups[50] (Friedman and Shechter[51] have given exceptions to this rule specially in the field of medium rings).

Preliminary investigations on the formation of carbenes from diazirines have already been made available. Frey and Stevens[52] recently reported the photolysis of cyclic diazomethane. Cyclic diazomethane was irradiated in the gaseous phase with light of wavelength

[50] For example: J. W. Powell and M. C. Whiting, *Tetrahedron* **12**, 168 (1961).
[51] L. Friedman and H. Shechter, *J. Am. Chem. Soc.* **83**, 3159 (1961).
[52] H. M. Frey and I. D. R. Stevens, *Proc. Chem. Soc. (London)* p. 79 (1962).

3130 Å. It was split into nitrogen and methylene [Eq. (59)]. In the absence of other reactive substances, the methylene reacted with more diazirine (**67**) to give ethylene [Eq. (60)]. The methylene from



(59)

(67)

(60)

compound **67** is probably in the singlet state. The addition to *trans*-butene-2 was stereospecific to give *trans*-1,2-dimethylcyclopropane. Simultaneously, *trans*-2-pentene and 2-methyl-2-butene were formed by insertion in the CH-bond. Methylene from cyclic diazomethane corresponds in energy content to that formed from linear diazomethane and in selectivity to the less energetic methylene from ketene.[52]

The methylethylcarbene which is formed thermally from methylethyldiazirine at 160°C gives the same products[53] as that from butanone *p*-toluenesulfonylhydrazone and bases in aprotic solvents.[54] However, photolysis of the same diazirine gives a different mixture of C_4H_8 hydrocarbons. Considerable amounts of 1-butene are formed, the *trans*-butene content is reduced by half, and the amount of methyl cyclopropane increased fivefold.[53]

The action of strong reducing agents on diazirines leads to basic products. Diaziridines can be detected as intermediates in the reaction. The reduction of 3,3-diethyldiazirine to 3,3-diethyldiaziridine [Eq. (61)][46] serves as a proof of structure of the diazirines.

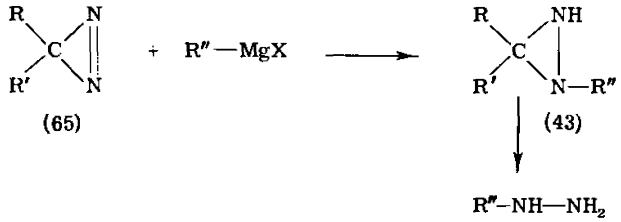
(61)

Because the diaziridines can easily be further reduced, their isolation from the reduction of the diazirines is only possible in poor

[53] H. M. Frey and I. D. R. Stevens, *J. Am. Chem. Soc.* **84**, 2647 (1962).
[54] L. Friedman and H. Shechter, *J. Am. Chem. Soc.* **81**, 5512 (1959).

yields. In the catalytic hydrogenation of 3,3-pentamethylenediazirine (**68**), after the uptake of 1 mole of hydrogen, only 13% of 3,3-pentamethylenediaziridine could be isolated. By careful reduction with sodium amalgam the yield was 35%.[32] On complete reduction, ammonia and a primary amine are obtained; thus, compound **68** yields ammonia and cyclohexylamine. The reduction of cyclic diazomethane gave ammonia but only small quantities of methylamine.[41]

A class of compounds which react smoothly with diazirines are the Grignard reagents. All investigated diazirines add Grignard reagents instantly at 0°C to the NN double bond yielding 1-alkyl-diaziridines [Eq. (62)].[32,41,44]



(62)

Thus the diazirines could be related by a smooth reaction to a well investigated class of compounds. The three-membered ring structure of the diazirines was thus largely confirmed. They can be obtained from compounds which certainly have a three-membered ring structure [Eq. (54)] and are easily convertible into compounds which have equally well confirmed three-membered ring structures. The structure of the 1-alkyl-diaziridines (**43**) obtained by the Grignard reaction were confirmed by identification with known compounds, usually prepared by the reaction of Schiff's bases with chloramine [Eq. (32)]. The results of some of these reactions are collected in Table XII.

The 1-alkyl-diaziridines can easily be hydrolyzed to alkyl hydrazines. Hence alkyl hydrazines are easily available from Grignard reagents and thus from alkyl halides. The three last examples of Table XII show the yield of alkyl hydrazine calculated on the diazirine used. The reaction has preparative interest because the alkylation of hydrazine with alkyl halides only gives monoalkyl hydrazines in exceptional cases.[55]

The addition of aromatic Grignards to diazirines is also possible:

[55] O. Westphal, *Ber. deut. chem. Ges.* **74**, 759 (1941).

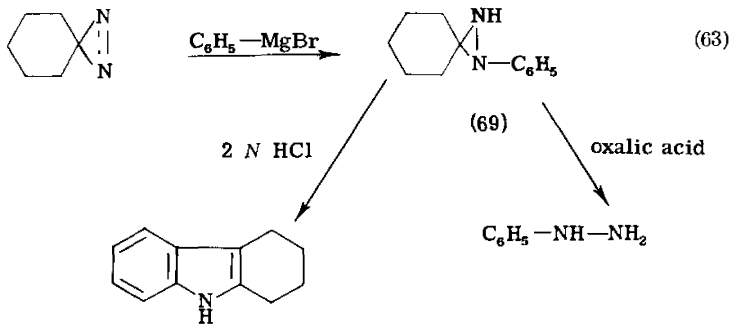
TABLE XII

1-ALKYL-DIAZIRIDINES FROM DIAZIRINES AND GRIGNARD COMPOUNDS[a]

Diazirine		Grignard compound,	Yield	
R	R′	R″	(%)	Ref.
Methyl	Methyl	Cyclohexyl	62	32[b]
	3,3-Pentamethylene	Cyclohexyl	86	32, 47[b]
H	H	Cyclohexyl	50[c]	41[b]
Methyl	H	Ethyl	69	41[b]
n-Propyl	H	Cyclohexyl	55[c]	41
	3,3-Pentamethylene	*n*-Propyl	88[d]	44
	3,3-Pentamethylene	*i*-Propyl	95[d]	44
	3,3-Pentamethylene	Benzyl	85[d]	44

[a] Prepared according to Eq. (62).
[b] Identified by comparison with an authentic sample.
[c] Yield of 1-alkyl-diaziridine, calculated on the diazirine which was not isolated.
[d] Yield of the alkyl hydrazine prepared by hydrolysis of the 1-alkyl-diaziridine (calculated on diazirine).

phenylmagnesium bromide reacts with 3,3-pentamethylenediazirine [Eq. (63)] to give the isomeric phenylhydrazone (**69**) in 60% yield.



(63)

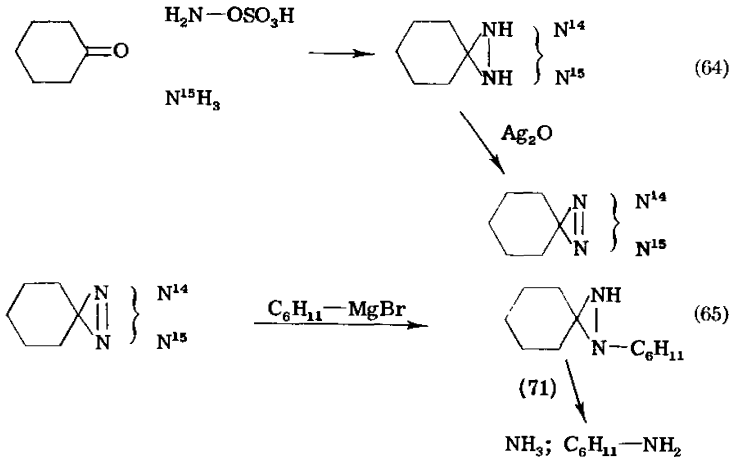
By hydrolysis of **69** with oxalic acid, phenylhydrazine is obtained, whereas heating with hydrochloric acid gives tetrahydrocarbazole (**70**).[32]

Metalloorganic compounds of zinc, cadmium, and lithium can be added, just as the Grignard compounds, to the NN double bond of diazirines.[56]

[56] E. Schmitz and R. Ohme, German Patent 1,134,083 (Aug. 2, 1962/Feb. 14, 1961).

D. Proof of Structure of Diazirines by N^{15}-Labeling

A Grignard reagent on reaction with a diazirine [Eq. (62)] can choose between two equivalent nitrogen atoms. The three-membered ring structure can thus be tested by N^{15} labeling. A cyclic diazo compound with a labeled N-atom was prepared from cyclohexanone, N^{15}-ammonia, and unlabeled hydroxylamine-*O*-sulfonic acid and followed by dehydrogenation [Eq. (64)]. By reaction with cyclohexylmagnesium bromide the chemical equivalence of the nitrogen atoms was removed [Eq. (65)]. The 1-cyclohexyl-3,3-pentamethylene-



diaziridine (**71**) was degraded reductively to cyclohexylamine and ammonia. The N^{15} labeling of compound **71** had been shared equally between the ammonia and the cyclohexylamine which were obtained as the final products of the reaction.[36,57] Because an exchange of the labeling between ammonia and hydroxylamine-*O*-sulfonic acid could be eliminated, the complete equivalence of the nitrogen atoms in pentamethylenediazirine is proved by the isotopic experiments.

The proof of the three-membered structure of the diazirines concludes the discussion on the three-membered ring structure of the aliphatic diazo compounds. The known linear aliphatic diazo compounds and the newly prepared cyclic diazo compounds (diazirines) are two independent classes of compounds completely different in their physical and chemical properties. An interconversion of the linear and cyclic diazo compounds has not so far been possible.

[57] E. Schmitz and R. Ohme, *Kernenergie* **5**, 357 (1962).

Free-Radical Substitutions of Heteroaromatic Compounds

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I. Introduction

The reactions to be discussed may be represented by Eq. (1), where heterocyclic-H is an aromatic heterocyclic compound and R· is a free radical. The reaction is a substitution in that R replaces H, but

$$\text{heterocyclic-H} + \text{R}\cdot \rightarrow \text{heterocyclic-R} + \text{H}\cdot \qquad (1)$$

whereas the attacking radical may usually be correctly described as "free," the displaced hydrogen atom is normally removed from the aromatic nucleus by a second radical.

Free-radical substitutions of heterocyclic compounds have been carried out with alkyl, aryl, and hydroxyl radicals in solution and with halogen atoms in the gas phase. Of these, arylations have been the most extensively investigated.

II. Arylation

A. Sources of Aryl Radicals

A number of methods are available for generating aryl radicals. They have been reviewed recently,[1] as has the evidence that the processes result in the generation of free aryl radicals.[1,2] Those methods which have been used for the arylation of heterocyclic compounds are described here, and their applications to the arylation of specific heterocycles are discussed and tabulated in Section II,C,D and E.

1. *Aryl Radicals from Compounds Containing the Azo Linkage*

Many compounds of general type Ar—N=N—X can be thermally decomposed to aryl radicals, the driving force for the reaction being, at least in part, the stability of the nitrogen molecule.

a. Diazonium Salts. The thermal decomposition of solid diazonium salts gives aryl radicals[3-5]:

$$Ar—N_2^+Cl^- \rightarrow Ar\cdot + N_2 + Cl\cdot \qquad (2)$$

Modifications of this method, such as the use of the more stable diazonium trifluoroacetates[6] and the decomposition of benzenediazonium zincichloride with zinc dust,[7] have been used as sources of aryl radicals, although not in the arylation of heterocyclic compounds. Pyridine, quinoline, and thiophene can be phenylated by treatment with benzenediazonium chloride and aluminum trichloride.[8]

b. The Gomberg Reaction. When an aqueous solution of a diazonium salt is treated with base in the presence of an aromatic compound, the unstable covalent hydroxide is formed and decomposes to free radicals, Eq. (3), which react with the aromatic compound.

$$Ar—N_2^+X^- + OH^- \rightarrow Ar—N=N—OH \rightarrow Ar\cdot + N_2 + \cdot OH \qquad (3)$$

[1] G. H. Williams, "Homolytic Aromatic Substitution." Pergamon Press, London, 1960.
[2] C. Walling, "Free Radicals in Solution." Wiley, New York, 1957.
[3] H. A. H. Pray, *J. Phys. Chem.* **30**, 1417, 1477 (1926).
[4] C. E. Waring and J. R. Abrams, *J. Am. Chem. Soc.* **63**, 2757 (1941).
[5] R. Möhlau and R. Berger, *Ber. deut. chem. Ges.* **26**, 1196 (1893).
[6] M. R. Pettit and J. C. Tatlow, *J. Chem. Soc.* p. 1941 (1954).
[7] R. O. C. Norman and W. A. Waters, *J. Chem. Soc.* p. 167 (1958).
[8] R. Möhlau and R. Berger, *Ber. deut. chem. Ges.* **26**, 1994 (1893).

This method (the Gomberg reaction) has been used more than any other in the arylation of heterocyclic compounds (see Table III). The aromatic compound to be substituted is normally immiscible with water and the reaction has to be carried out in a two-phase system consisting of an aqueous solution of the diazonium salt and the aromatic compound (if it is a liquid) or a solution of the compound in an organic solvent (if it is a solid). The success of the procedure then depends on the diazo hydroxide being extracted from the aqueous into the organic phase as fast as it is formed. Yields are generally low and are rarely above 30%.[9] The process is more efficient when the organic compound is water-soluble: for example, pyridine gives the three phenylpyridines in 40% over-all yield.[10] Moreover, when the aromatic compound is itself basic, as pyridine is, addition of an inorganic hydroxide is unnecessary and there are fewer possible by-products.

c. Acylarylnitrosamines. A process which is closely related to the Gomberg reaction and is usually more efficient is the decomposition of acylarylnitrosamines in organic solvents. Reaction takes place by rearrangement to the diazo ester which then undergoes homolytic fission, Eq. (4).[11] The *p*-nitrophenylation of pyridine and pyrimidine[12]

$$Ar—N(NO)—CO—CH_3 \rightarrow Ar—N=N—O—CO—CH_3 \rightarrow Ar\cdot + N_2 + \cdot O—CO—CH_3 \qquad (4)$$

and the arylation of furan[13] have been effected in over-all yields of 20–30% by this method.

A modification of the Gomberg reaction involves the use of acetate instead of hydroxide ions,[13] the process then being analogous to the decomposition of acylarylnitrosamines.

d. Other Azo Compounds. The thermal decomposition of phenylazotriphenylmethane to phenyl and triphenylmethyl radicals[14] has been used to phenylate pyridine.[15] These azo compounds also give free

[9] W. E. Bachmann and R. A. Hoffman, *in* "Organic Reactions" (R. Adams *et al.*, eds.), Vol. 2, p. 224. Wiley, New York, 1944.
[10] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.* p. 349 (1940).
[11] D. H. Hey, J. Stuart-Webb, and G. H. Williams, *J. Chem. Soc.* p. 4657 (1952).
[12] B. Lythgoe and L. S. Rayner, *J. Chem. Soc.* p. 2323 (1951).
[13] A. W. Johnson, *J. Chem. Soc.* p. 895 (1946).
[14] D. H. Hey, *J. Chem. Soc.* p. 1966 (1934).
[15] W. J. Adams, D. H. Hey, P. Mamalis, and R. E. Parker, *J. Chem. Soc.* p. 3181 (1949).

radicals on irradiation.[16] Triazenes of general type Ar—N=N—NR_2, which are readily prepared from diazonium salts and amines, are decomposed to aryl radicals by being heated to 90–100°C while hydrogen chloride is introduced; for example, the 2-naphthyl radical has been formed from 1,2′-naphthyl-3,3-dimethyltriazene and used to arylate pyridine.[17] Diazoaminobenzenes decompose to aryl radicals at 150–160°C.[18]

2. *Aryl Radicals from Peroxides*

The low bond-strength of the O—O bond renders peroxides susceptible to homolytic fission to give oxy radicals on heating. Diacyl peroxides give rise to acyloxy radicals[19] which then decompose to aryl radicals and carbon dioxide, Eq. (5). For example, dibenzoyl

$$(\mathrm{Ar—CO{-}{-}O})_2 \rightarrow 2\ \mathrm{Ar—CO{-}{-}O\cdot} \rightarrow 2\ \mathrm{Ar\cdot} + 2\ \mathrm{CO_2} \qquad (5)$$

peroxide decomposes unimolecularly with a half-life of about 5 hr at 80°C.[20] (The kinetics of such peroxide decompositions are often complicated because of induced decomposition in which the solvent takes part.[21]) If the peroxide is decomposed in the presence of an aromatic compound of very high reactivity toward radicals, acyloxylation occurs before the acyloxy radical decomposes. This is usually the case with polycyclic aromatic systems but not with the less reactive monocyclic compounds (cf. Section III,C). Thus anthracene reacts with dibenzoyl peroxide to give 9-benzoyloxyanthracene,[22] whereas pyridine,[23] quinoline,[23] and benzothiazole[24] are phenylated by the reagent.

The production of aryl radicals from peroxides normally provides a cleaner method of arylation than the methods based on the decomposition of azo and diazo compounds, and, in the case of benzenoid compounds, better yields of arylated products are obtained.[25] The

[16] R. Huisgen and H. Nakaten, *Ann.* **586**, 70 (1954).
[17] J. Elks and D. H. Hey, *J. Chem. Soc.* p. 441 (1943).
[18] R. L. Hardie and R. H. Thompson, *J. Chem. Soc.* p. 1286 (1958).
[19] G. S. Hammond and L. M. Soffer, *J. Am. Chem. Soc.* **72**, 4711 (1950).
[20] A. T. Blomquist and A. J. Buselli, *J Am. Chem. Soc.* **73**, 3883 (1951).
[21] K. Nozaki and P. D. Bartlett, *J. Am. Chem. Soc.* **68**, 1686 (1946); W. E. Cass, *J. Am. Chem. Soc.* **68**, 1976 (1946).
[22] I. M. Roitt and W. A. Waters, *J. Chem. Soc.* p. 2695 (1952).
[23] D. H. Hey and E. W. Walker, *J. Chem. Soc.* p. 2213 (1948).
[24] A. Nagasaka, R. Oda, and S. Nukina, *Kôgyô Kagaku Zasshi* **57**, 227 (1954).
[25] G. H. Williams, "Homolytic Aromatic Substitution," p. 34. Pergamon Press, London, 1960.

yields from pyridine and its derivatives, however, are usually low,[23] partly as a result of the oxidation of the heterocycle to its *N*-oxide.[26]

3. *Other Methods*

Phenyl radicals can be generated by the thermal decomposition of lead tetrabenzoate,[27] phenyl iodosobenzoate,[28] and diphenyliodonium hydroxide,[29] and by the electrolysis of benzoic acid.[30] These methods have been employed in the arylation of aromatic compounds, including heterocycles. A method of promise which has not been applied to the arylation of heterocycles is the formation of aryl radicals by the photolysis of aromatic iodides at 2537 Å.[31]

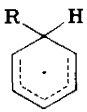
B. Mechanism of Arylation

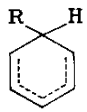
There has been relatively little work on the mechanism of arylation of heterocyclic compounds, but the arylation of homocyclic compounds has been studied in great detail. Those mechanistic aspects of the reactions with heterocycles which have been examined parallel closely the corresponding aspects of the reactions of homocycles, and there is

(i) $\mathrm{R\cdot + Ar—H \longrightarrow R—H + Ar\cdot}$ (6)

$\mathrm{Ar\cdot + R\cdot \longrightarrow Ar—R}$ (7)

(ii) $\mathrm{R\cdot + Ar—H \longrightarrow R—Ar + H\cdot}$ (8)

(iii) $\mathrm{R\cdot + Ph—H} \longrightarrow$  (9)

 $\longrightarrow \mathrm{Ph—R + H\cdot}$ (10)

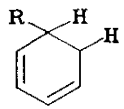
Scheme 1

[26] K. H. Pausacker, *Australian J. Chem.* **11**, 200 (1958).
[27] D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.* p. 2747 (1954).
[28] D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.* p. 1475 (1956).
[29] R. B. Sandin and R. K. Brown, *J. Am. Chem. Soc.* **69**, 2253 (1947).
[30] F. Fichter and H. Stenzl, *Helv. Chim. Acta* **22**, 970 (1939).
[31] W. Wolf and N. Kharasch, *J. Org. Chem.* **26**, 283 (1961).

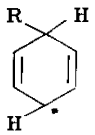
no reason to suppose that the mechanisms of arylation of the two groups of compounds differ in any fundamental way. Discussion of the mechanism of arylation is, therefore, based largely on studies of the arylation of benzenoid compounds.

Three possible routes have been considered for the arylation of a benzenoid compound (see Scheme 1).

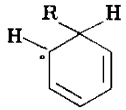
In (i), a hydrogen atom is abstracted from the aromatic molecule, the resulting aromatic radical then coupling with a second attacking radical. Path (ii) is a synchronous displacement of a hydrogen atom by the attacking radical. Path (iii) consists of the addition of the radical to the aromatic nucleus to give an adduct in which the unpaired electron is delocalized over the residual aromatic system [see structures (1–3)], followed by elimination of a hydrogen atom. This path has two variants, depending on whether (a) the addition or (b) the loss of the hydrogen atom is the rate-determining step.



(1)



(2)



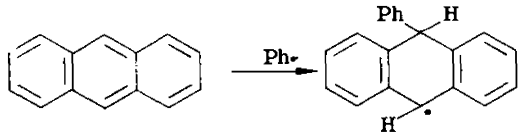
(3)

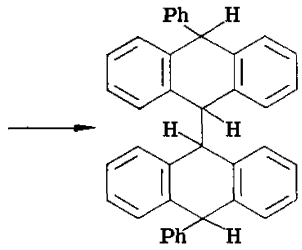
A distinction between these four possibilities can be made on the basis of the kinetic isotope effect. There is no isotope effect in the arylation of deuterated[32] or tritiated[33,34] benzenoid compounds with dibenzoyl peroxide, thereby ruling out mechanisms in which a C—H bond is broken in the rate-determining step of the substitution. Paths (ii) and (iii,b) are therefore eliminated. In path (i) the first reaction, Eq. (6), is almost certain to be rate-determining, for the union of two radicals, Eq. (7), is a process of very low activation energy, while the abstraction in which a C—H bond is broken would require activation.[35] More significant evidence against this path is that dimers, Ar_2, should result from it, yet they are never isolated. For instance, no 4,4′-dinitrobiphenyl is formed during the phenylation of

[32] R. I. Milyutinskaya, Kh. S. Badgasaryan, and E. A. Izrailevich, *Zhur. Fiz. Khim.* **31**, 1019 (1957).
[33] R. J. Convery and C. C. Price, *J. Am. Chem. Soc.* **80**, 4101 (1958).
[34] Shih Chang, D. H. Hey, and G. H. Williams, *J. Chem. Soc.* p. 1871 (1959).
[35] J. O. Hirschfelder, *J. Chem. Phys.* **9**, 645 (1941).

nitrobenzene with dibenzoyl peroxide, although the attacking radical dimerizes to give biphenyl in 3–4% yield.[36]

The results are consistent with the rate-determining step being addition of the aryl radical to the aromatic ring, Eq. (9). Support for this mechanism is derived from the results of three other studies: (a) When *N*-nitrosoacetanilide is decomposed in pyridine, the benzene formed by abstraction of hydrogen from pyridine by phenyl radical accounts for only 1 part in 120 of the reaction leading to phenylpyridines.[37] (b) 9,9′,10,10′-Tetrahydro-10,10′-diphenyl-9,9′-bianthryl is formed in the reaction between phenyl radicals and anthracene, probably by the addition mechanism in Eq. (11).[7] Adducts are also formed in the reactions of benzyl radicals with anthracene[38] and acridine.[39]



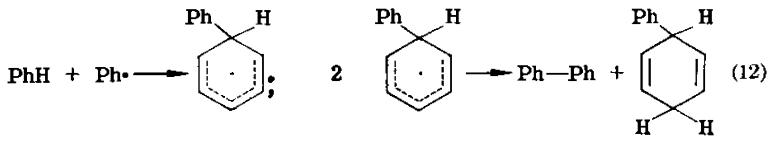


(11)

It is understandable that dihydro adducts should be formed by polycyclic compounds and not by benzene or pyridine, because the loss of aromatic resonance energy is smaller in the former than in the latter process. (c) When dibenzoyl peroxide is decomposed in very dilute solution (0.01 *M*) in benzene, 1,4-dihydrobiphenyl is produced as well as biphenyl, consistent with addition of the phenyl

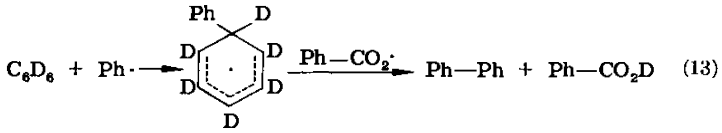
[36] D. F. DeTar, *J. Am. Chem. Soc.* **72**, 1028 (1950).
[37] R. Huisgen and G. Horeld, *Ann.* **562**, 137 (1949).
[38] A. L. J. Beckwith and W. A. Waters, *J. Chem. Soc.* p. 1001 (1957).
[39] W. A. Waters and D. H. Watson, *J. Chem. Soc.* p. 253 (1957).

radical to benzene followed by disproportionation of two adduct radicals, Eq. (12).[40]



(12)

This last result bears also on the mode of conversion of the adduct to the final substitution product. As written in Eq. (10), a hydrogen atom is eliminated from the adduct, but it is more likely that it is abstracted from the adduct by a second radical. In dilute solutions of the radical-producing species, this second radical may be the adduct itself, as in Eq. (12),[41] but when more concentrated solutions of dibenzoyl peroxide are employed, the hydrogen atom is removed by a benzoyloxy radical, for in the arylation of deuterated aromatic compounds the deuterium lost from the aromatic nucleus appears as deuterated benzoic acid, Eq. (13).[32] The over-all reaction for the phenylation of benzene by dibenzoyl peroxide may therefore be written as in Eq. (14).



(13)

$$(Ph—COO)_2 + Ph—H \rightarrow Ph—Ph + Ph—CO_2H + CO_2 \qquad (14)$$

C. Quantitative Studies

1. *Introduction*

As a result of most of the early work on the homolytic arylation of monosubstituted benzenoid compounds it was concluded that the attacking radical was directed to the *ortho* and *para* positions in the benzene ring regardless of the nature of the substituent. Similarly,

[40] D. F. DeTar and R. A. J. Long, *J. Am. Chem. Soc.* **80**, 4742 (1958).
[41] E. L. Eliel, S. Meyerson, Z. Welvart, and S. H. Wilen, *J. Am. Chem. Soc.* **82**, 2936 (1960).

from reactions on pyridine, normally only the 2- and 4-derivatives were produced. For example, 2- and 4-phenylpyridine were isolated from the electrolysis of benzoic acid in pyridine,[30] and 2- and 4-derivatives were obtained from the Gomberg reaction on pyridine using *para*-substituted benzenediazonium salts.[42] Later work, particularly that in which more sensitive and accurate physical methods of analysis such as spectrophotometry have been used, shows that these generalizations were incorrect. In reactions on benzenoid compounds and pyridine, the *ortho* and 2-derivatives, respectively, are usually the predominant products, whereas the *meta* and 3-derivatives are usually the next most abundant. In the earlier work, the least abundant *para* or 4-derivative, being the least soluble of the isomers, was often the most easily isolated. In discussing the quantitative results, therefore, the reports of greatest value are those derived from experiments in which the composition of the product was determined by a physical method. For heterocyclic compounds these reports relate mainly to the arylation of pyridine.

2. *Isomer Ratios*

The quantitative phenylation of pyridine has been studied by two groups of workers. Dannley and Gregg showed that 2-, 3-, and 4-phenylpyridine are formed in relative amounts 58:28:14 in the phenylation of pyridine with dibenzoyl peroxide, as estimated by infrared spectrophotometry.[43] Hey and his co-workers obtained the ratios shown in Table I for the phenylation of pyridine using four different sources of phenyl radicals.[44,45]

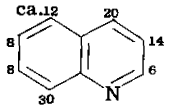
TABLE I
Isomer Distributions in the Phenylation of Pyridine

Radical source	Isomer distribution (%)		
	2-	3-	4-
Dibenzoyl peroxide	54	32	14
Lead tetrabenzoate	52	32.5	15.5
Phenyl iodosobenzoate	58	28	14
Phenylazotriphenylmethane (corrected[44])	53	31	16

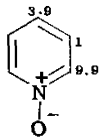
[42] E. C. Butterworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.* p. 355 (1940).
[43] R. L. Dannley and E. C. Gregg, *J. Am. Chem. Soc.* **76**, 2997 (1954).
[44] D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.* p. 3963 (1955).
[45] P. J. Bunyan and D. H. Hey, *J. Chem. Soc.* p. 3787 (1960).

The close similarity in the isomer ratios obtained from different sources of the phenyl radical suggests that the mechanism of arylation is independent of the nature of the reagent which generates the radical. This principle has been used in reverse in that the constancy of isomer ratios has been cited as evidence that the decomposition of lead tetrabenzoate gives free phenyl radicals.

The phenylation of quinoline with dibenzoyl peroxide was studied by Pausacker, who obtained all seven monophenylated quinolines in relative amounts shown in (4).[26] He also examined the phenylation of pyridine-*N*-oxide with diazoaminobenzene and obtained the results shown in (5).[46]



(4)



(5)

3. *Relative Reactivities*

The reactivity of pyridine relative to that of benzene has been measured using the competitive technique developed by Ingold and his schoool for corresponding studies of electrophilic aromatic substitution.[47] The validity of the method applied to free-radical reactions has been discussed.[48] Three sources of the phenyl radical have been used; the results obtained are set out in Table II.

From the relative reactivities, together with the isomer ratios for the phenylation of pyridine, it is possible to calculate the reactivity of each position in the pyridine ring compared with that of any one position in benzene (the partial rate factor). Thus, using the value of 1.04 for the relative reactivities obtained by Augood *et al.*[49] and the isomer ratios (2-, 58; 3-, 28; 4-, 14) obtained by Dannley and Gregg,[43] the partial rate factors for the three positions in pyridine are: 2-, 1.8; 3-, 0.87; 4-, 0.87. It is doubtful, however, whether much

[46] K. H. Pausacker, *J. Chem. Soc.* p. 18 (1961).
[47] C. K. Ingold, A. Lapworth, E. Rothstein, and D. Ward, *J. Chem. Soc.* p. 1959 (1931).
[48] G. H. Williams, "Homolytic Aromatic Substitution," p. 54. Pergamon Press, London, 1960.
[49] D. R. Augood, D. H. Hey, and G. H. Williams, *J. Chem. Soc.* p. 2094 (1952).

TABLE II
THE REACTIVITY OF PYRIDINE IN PHENYLATION[a]

Radical source	Temp. (°C)	Relative reactivity
Dibenzoyl peroxide	70	1.04
Dibenzoyl peroxide	80	1.5
N-Nitrosoacetanilide	20	1.0
Photolysis of triphenylbismuth	80	1.2

[a] Source: G. H. Williams, "Homolytic Aromatic Substitution," p. 57. Pergamon Press, London, 1960.

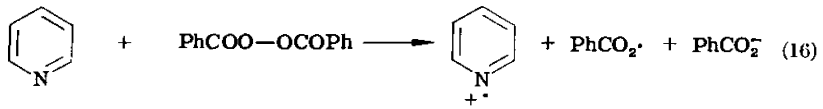
significance can be attached to these values, for two reasons. First, the derivation carries the implicit assumption that Eq. (15) is the only

$$\mathrm{Ph\cdot} + \mathrm{Ar{-}H} \rightarrow \mathrm{Ar}\begin{matrix}\mathrm{Ph}\\ \\ \mathrm{H}\end{matrix} \qquad (15)$$

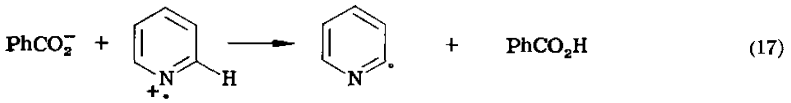
one involved in determining the isomer distribution. If the adduct radicals take part in side reactions, such as the disproportionation observed by DeTar and Long,[40] the isomer ratios, and therefore the partial rate factors, will have no particular meaning. Second, both pyridine-*N*-oxide and bipyridyls are formed during the decomposition of dibenzoyl peroxide in pyridine,[26] showing that pyridine is removed from the system by a reaction other than phenylation. The measured over-all reactivity of pyridine relatively to benzene is, therefore, probably a low estimate. It is, however, clear that, as with other homolytic aromatic substitutions,[1] the effect of the hetero atom is small compared with the corresponding effects in heterolytic aromatic substitution.

The two by-products mentioned in the foregoing which have been obtained from the reaction of dibenzoyl peroxide with pyridine evidently result from paths not available to benzenoid compounds. It has been suggested[26] that the bipyridyls are formed by nucleophilic displacement by nitrogen on one of the peroxy-oxygen atoms, Eq. (16), giving a radical cation from which a proton is abstracted by benzoate ion, Eq. (17). Two of the resulting pyridyl radicals couple to give a bipyridyl. Analogous heterolyses of peroxides by basic nitrogen have been previously reported.[50]

[50] L. Horner, *J. Polymer Sci.* **18**, 438 (1955).

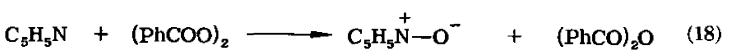


(16)



(17)

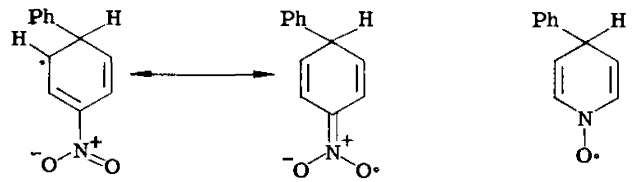
Pyridine-*N*-oxide may be formed in a manner analogous to the reaction of dibenzoyl peroxide with tertiary phosphines, i.e., Eq. (18).[51]



(18)

4. *Interpretation of Results*

The factors which control the orientation of the entering radical in the arylation both of monosubstituted benzenoid compounds and of heterocyclic compounds are not fully understood. In certain cases the results can be rationalized: for example, nitrobenzene is predominantly *ortho, para* directing (*o*-, 62.5; *m*-, 9.8; *p*-, 27.7%[52]), the *ortho*:*para* ratio being close to the statistical value of 2:1. This is consistent with the ability of the nitro group to delocalize the unpaired electron in the adduct radical, and hence in the rate-determining transition state leading to that radical, when attack occurs at the *ortho* or *para* positions [see structures (6) and (7)]. The same argument can be applied to the arylation of pyridine-*N*-oxide: the oxygen atom can increase the extent of delocalization when attack is at the 2- or 4-positions, as shown in structure (8).



(6) (7) (8)

[51] D. B. Denney and M. A. Greenbaum, *J. Am. Chem. Soc.* **79**, 979 (1957).
[52] G. H. Williams, "Homolytic Aromatic Substitution," p. 68. Pergamon Press, London, 1960.

In many cases, however, the *ortho* isomer is the predominant product, and it is the *meta*:*para* ratio which is close to the statistical value, in reactions both on benzenoid compounds[52] and on pyridine.[43-45] There has been no satisfactory explanation of this feature of the reaction. One theory, which lacks verification, is that the radical first forms a complex with the aromatic compound at the position of greatest electron density; that this is invariably either the substituent or the position *ortho* to the substituent, depending on whether the substituent is electron-attracting or -releasing; and that when the preliminary complex collapses to the σ-complex, the new bond is most likely to be formed at the *ortho* position.[53] For heterocyclic compounds such as pyridine it is possible that the phenyl radical complexes with the nitrogen atom and that a simple electronic reorganization forms the σ-complex at the 2-position.

D. Preparative Studies

Free-radical arylation of heterocyclic compounds is a relatively inefficient process in which yields of particular products greater than 50% are rare. This is the inevitable result of the high reactivity and low selectivity of aryl radicals: not only is it usual for the heterocyclic compound to be attacked at each of its available positions, but, as shown in preceding sections, other by-products are numerous. Nevertheless, the method often presents the only short route to a given compound and it has been widely applied. Preparative uses are grouped in this section under the heading of the heterocyclic system concerned.

1. *Pyridine*

Pyridine has been phenylated with the following free-radical sources: benzenediazonium chloride with aluminum trichloride[8]; the Gomberg reaction[10,54]; phenylhydrazine and metal oxides[55]; *N*-nitrosoacetanilide[56]; dibenzoyl peroxide[23]; phenylazotriphenylmethane[15]; diphenyliodonium hydroxide[20]; and electrolysis of benzoic acid.[30] Although 2-phenylpyridine usually accounts for over 50% of the total phenylated product, each of the three phenyl derivatives can be obtained from the reaction by fractional recrystallization of the

[53] C. S. Rondestvedt and H. S. Blanchard, *J. Org. Chem.* **21**, 229 (1956).
[54] M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.* **46**, 2339 (1924).
[55] R. L. Hardie and R. H. Thompson, *J. Chem. Soc.* p. 2512 (1957).
[56] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.* p. 372 (1940).

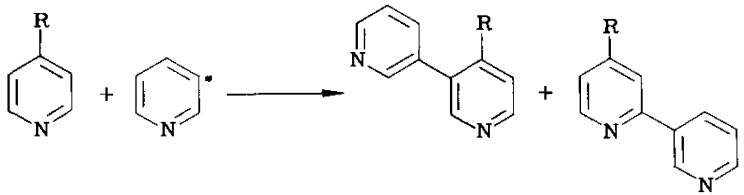
picrates. The highest yield obtained is 60% overall, by the decomposition of *N*-nitrosoacetanilide in pyridine[56]; somewhat lower yields are obtained using the Gomberg reaction (40%)[10] and dibenzoyl peroxide (35%).[23] In one case in which all three derivatives are obtained (the decomposition of phenylazotriphenylmethane in pyridine), the 2-isomer is the least abundant.[15]

The method most commonly used for the arylation of pyridine has been the Gomberg reaction. It has been developed by Heilbron, Hey, and their collaborators, and consists of the slow addition of an aqueous solution of the diazonium salt to excess of pyridine at temperatures between 20 and 70°C. Arylpyridines are formed in total yields varying between 20 and 80%, depending on the diazonium salt.[10] In this way phenylpyridines substituted with the following groups in the benzenoid ring have been obtained: *o*-, *m*-, and *p*-nitro[10]; *p*-chloro, *p*-bromo, *p*-ethoxy, and *p*-carboxy[42]; *o*-, *m*-, and *p*-methoxy[57]; *m*- and *p*-phenyl.[58] Hey and his colleagues have also applied the diacyl peroxide method to the synthesis of arylpyridines containing the following aryl groups: *p*-chlorophenyl, *p*-anisyl, 1-naphthyl, and 2-naphthyl.[23] The three nitrobenzoyl peroxides, however, failed to yield nitrophenylpyridines.[23]

In a search for new spasmolytics, Heilbron and Hey and their co-workers synthesized a number of pyridylquinolines by coupling diazotized aminoquinolines with pyridine.[59,60] Pyridine has also been substituted by the 3-pyridyl radical in the Gomberg reaction, the 2- and 3-substituted products being obtained in 55 and 5% yield, respectively, together with a third product obtained in 20% yield which was tentatively formulated as the 4-isomer.[61] The same radical was coupled with 4-methyl- and 4-ethyl-pyridine and gave in each case mixtures of the two possible substitution products in which the radical had coupled predominantly with the carbon atom of pyridine adjacent to the alkyl substituent, as shown in Eq. (19).[61]

On the other hand, the 3-quinolyl radical (from diazotized 3-amino-

[57] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.* p. 358 (1940).
[58] I. M. Heilbron, D. H. Hey, and A. Lambert, *J. Chem. Soc.* p. 1279 (1940).
[59] H. Coates, A. H. Cook, I. M. Heilbron, D. H. Hey, A. Lambert, and F. B. Lewis, *J. Chem. Soc.* p. 401 (1943); R. A. Abramovitch, *J. Chem. Soc.* p. 3839 (1954).
[60] A. H. Cook, I. M. Heilbron, D. H. Hey, A. Lambert, and A. Spinks, *J. Chem. Soc.* p. 404 (1943).
[61] R. L. Frank and J. V. Crawford, *Bull. soc. chim. France* p. 419 (1958).



(19)

(*a*): R = Me, 55% (*b*): R = Me, 15%
= Et, 55% = Et, 14%

quinoline) substituted ethyl isonicotinate at the 2-position (i.e., that adjacent to the hetero atom).[62]

2. *Quinoline*

The phenylation of quinoline with dibenzoyl peroxide has been reported to give a mixture of 4- and 5-phenylquinoline which can be separated by the fractional recrystallization of their picrates.[23] In a later investigation, the other five phenylquinolines have also been identified among the products, the relative reactivities of the nuclear positions being: 8- > 4- > 3-, 5- > 2-, 6-, 7-.[26]

3. *Six-Membered Heterocycles Containing Two Nitrogen Atoms*

The phenylation of pyridazine and quinoxaline has been carried out using dibenzoyl peroxide, *N*-nitrosoacetanilide, and benzenediazonium hydroxide as the sources of phenyl radical, the first two methods giving very much better yields than the third.[63] The most reactive positions in these ring systems are the 4-position in pyridazine and the 2-position in quinoxaline. Phthalazine has been phenylated with *N*-nitrosoacetanilide, giving a low yield of 5-phenylphthalazine, but the main product from cinnoline in this reaction was 4,4′-bicinnolyl, although a small quantity of 4-phenylcinnoline was obtained.[63] Pyrimidine has been arylated only with the 4-nitrophenyl radical, substitution occurring at the 2- and 4-positions.[12]

4. *Five-Membered Heterocycles*

The arylation of furan by the Gomberg reaction has been carried out using a number of differently substituted diazonium salts. In

[62] D. H. Hey and J. M. Williams, *J. Chem. Soc.* p. 1678 (1950).
[63] C. M. Atkinson and C. J. Sharpe, *J. Chem. Soc.* p. 3040 (1959).

TABLE III

CONDITIONS AND PRODUCTS IN THE ARYLATION OF HETEROCYCLIC COMPOUNDS

Heterocyclic compound	Aryl radical	Source	Total arylation (%)	Positions of substitution (and yields where quoted)	Ref.
Pyridine	phenyl	$Ph—N_2^+$	40	2 (10%); 3 (4%); 4 (4%)	10
	phenyl	*N*-Nitrosoacetanilide	60	2 (ca. 14%); 3 (ca. 6%); 4 (ca. 6%)	56
	phenyl	Peroxide	35	2, 3, 4	23
	phenyl	Phenylazotriphenylmethane	—	4 > 3 > 2	15
	phenyl	Triazene	51	2 > 3 > 4	17
	4-chlorophenyl	$Ar—N_2^+$	—	2 > 4	42
	4-bromophenyl	$Ar—N_2^+$	—	2 > 4	42
	4-ethoxyphenyl	$Ar—N_2^+$	—	2 > 4	42
	4-carboxyphenyl	$Ar—N_2^+$	—	2 > 4	42
	2-anisyl	$Ar—N_2^+$	50	2, 3, 4	57
	3-anisyl	$Ar—N_2^+$	54	2, 4	57
	4-anisyl	$Ar—N_2^+$	30	2, 4	57
	2-nitrophenyl	$Ar—N_2^+$	35	2 = 3 > 4	10
	3-nitrophenyl	$Ar—N_2^+$	35	2, 3, 4	10
	4-nitrophenyl	$Ar—N_2^+$	75	2 (24%); 3 (9%); 4 (4.5%)	10
	4-nitrophenyl	Triazene	50	2, 3, 4	17
	3-biphenyl	$Ar—N_2^+$	—	2, 4	58
	4-biphenyl	$Ar—N_2^+$	—	2, 4	58
	4-nitrophenyl	Acylarylnitrosamine	—	2 (14.5%); 3 (5%); 4 (2.5%)	12
	4-chlorophenyl	Peroxide	27	2, 4	23
	4-anisyl	Peroxide	27	2, 4	23
	1-naphthyl	Peroxide	(low)		23
	2-naphthyl	Peroxide	(low)	2, 3, 4	23
	2-naphthyl	Triazene	41	2, 3, 4	17
	3-pyridyl	$Ar—N_2^+$	—	2 (55%); 3 (5%); ? 4 (20%)	61
	3-quinolyl	$Ar—N_2^+$	44	2 > 4	59
	5-quinolyl	$Ar—N_2^+$	26	2	59
	8-quinolyl	$Ar—N_2^+$	14	2, (3), (4)	59
	8-(6-α-pyridyl)quinolyl	$Ar—N_2^+$	21		60
4-Methylpyridine	3-pyridyl	$Ar—N_2^+$	—	2 (15%); 3 (55%)	61
4-Ethylpyridine	3-pyridyl	$Ar—N_2^+$	—	2 (14%); 3 (55%)	61
4-Carbethoxypyridine	3-quinolyl	$Ar—N_2^+$	—	2	62
Quinoline	phenyl	Peroxide	—	4 (7%) > 5	23
	phenyl	Peroxide	—	8 > 4 > 3, 5 > 2, 6, 7	26
Pyridazine	phenyl	Acylarylnitrosamine	—	4 (26%)	63
	phenyl	Peroxide	—	4 (14%)	63
	phenyl	$Ar—N_2—OH$	—	4 (2%)	63
Quinoxaline	phenyl	Acylarylnitrosamine	—	2 (15.5%); 5 (2.3%); 6 (0.35%)	63
	phenyl	Peroxide	—	2 (17.4%); 5 (5.4%); 6 (0.35%)	63
	phenyl	$Ar—N_2—OH$	—	2 (1.9%); 5 (0.5%); 6 (0.05%)	63
Phthalazine	phenyl	Acylarylnitrosamine	—	5 (6%)	63
Cinnoline	phenyl	Acylarylnitrosamine	—	4	63
Pyrimidine	4-nitrophenyl	Acylarylnitrosamine	—	2 (10%); 4 (14%)	12
Furan	phenyl	$Ar—N_2^+ + OH^-$	—	2 (22%)	13
	4-chlorophenyl	$Ar—N_2^+ + OH^-$	—	2 (29%); 3 (0.7%)	13
	4-nitrophenyl	$Ar—N_2^+ + OAc^-$	—	2 (20%)	13
	3-chlorophenyl	$Ar—N_2^+ + OH^-$	—	2 (16%)	13
	4-bromophenyl	$Ar—N_2^+ + OH^-$	—	2 (15%)	13
	1-naphthyl	$Ar—N_2^+ + OAc^-$	—	2 (18%)	13
2-Furoic acid	4-chlorophenyl	$Ar—N_2^+ + OAc^-$	—	5 (20%)	65
	4-bromophenyl	$Ar—N_2^+ + OAc^-$	—	5	65
	3-nitrophenyl	$Ar—N_2^+ + OAc^-$	—	5	65
	4-nitrophenyl	$Ar—N_2^+ + OAc^-$	—	5	65
Thiophene	4-tolyl	$Ar—N_2^+ + OH^-$	—	2 (20%)	64
	4-chlorophenyl	$Ar—N_2^+ + OH^-$	—	2 (30%)	64
Benzothiazole	phenyl	Peroxide	—	2 (3%) > 4	24

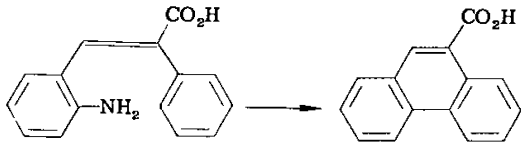
every case the 2-position is the more reactive, the 3-substituted derivative usually not being isolated.[13]

There is an early report that thiophene reacts at the 3-position in phenylation with benzenediazonium chloride and aluminum trichloride,[8] but in the Gomberg reaction thiophene has been found to substitute mainly at the 2-position both with *p*-tolyl and with *p*-chlorophenyl radicals.[64] Benzothiazole is phenylated at the 2-position in low yield by dibenzoyl peroxide; a small quantity of the 4-isomer is also obtained.[24]

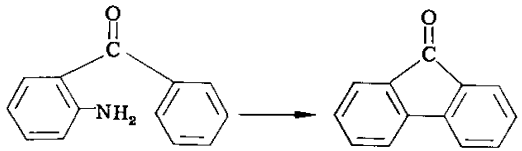
The data pertaining to arylations are gathered in Table III, except that in cases where a compound has been arylated by more than one method, only the reports referring to better yields of products are included.

E. Internuclear Cyclization

The Pschorr reaction, originally applied to the synthesis of phenanthrene and its derivatives,[66,67] has been adapted to the formation of new heterocyclic systems.[67] In its original form, it consisted of treating a diazonium salt with copper powder in acid solution: in this way, *trans*-*o*-amino-α-phenylcinnamic acid was converted into phenanthrene-9-carboxylic acid, Eq. (20). Variants of the reaction include cyclizations such as that in Eq. (21). The reaction may be homolytic



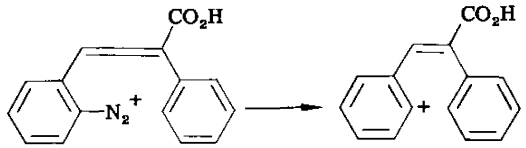
(20)



(21)

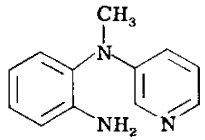
[64] N. G. Buu-Hoi and N. Hoán, *Rec. trav. chim.* **69**, 1455 (1950).
[65] K. B. L. Mathur and H. S. Mehra, *J. Chem. Soc.* p. 2576 (1961).
[66] R. Pschorr, *Ber. deut. chem. Ges.* **29**, 496 (1896).
[67] D. F. DeTar, *in* "Organic Reactions" (R. Adams *et al.*, eds.), Vol. 9, p. 409. Wiley, New York, 1957.

or heterolytic, depending on the conditions in which it is carried out. In the acid-catalyzed procedure, nitrogen is lost from the diazonium cation, giving an aryl cation which reacts with the adjacent aromatic ring to displace a proton, e.g. Eq. (22).[68] In alkaline conditions and



(22)

in the presence of copper, on the other hand, the reaction is almost certainly homolytic, and similar to the Gomberg reaction. This conclusion[69] has been substantiated by studying the effect on the yield of substituents in the ring in which substitution occurs. If the reaction were heterolytic, electron-attracting substituents should reduce the ease of reaction and lower the yield, whereas electron-releasing substituents should have the opposite effect. In fact, substituents are essentially without effect on the yield from the reaction.[70] Further, Hey and Osbond showed that the Pschorr reaction can be carried out quickly and efficiently on *trans*-*o*-amino-α-phenylcinnamic acid by treating a suspension of the dry diazonium chloride in acetone with copper powder,[71] which shows obvious analogy to the homolytic phenylation procedure of Norman and Waters, who used zinc in place of copper.[7] Finally, support for the homolytic mechanism comes from the finding that the diazonium salt from 2-amino-*N*-methyl-*N*-3′-pyridylaniline (**9**) is cyclized with copper powder to a mixture of the carbolines (**10**) and (**11**) in about the same total yield as the corresponding cyclization of *N*-(3-amino-2-pyridyl)-*N*-methylaniline (**12**) to *ind*-*N*-methyl-α-carboline (**13**).[72] If the reaction were hetero-



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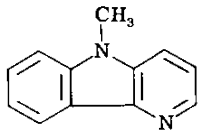

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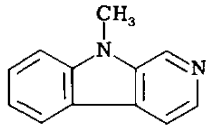
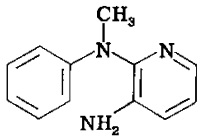


(11) 25.5%

[68] D. F. DeTar and A. R. Ballentine, *J. Am. Chem. Soc.* **78**, 3916 (1956), and references therein.
[69] D. F. DeTar and S. V. Sagmanli, *J. Am. Chem. Soc.* **72**, 965 (1950).
[70] D. H. Hey and J. M. Osbond, *J. Chem. Soc.* p. 3172 (1949).
[71] D. H. Hey and J. M. Osbond, *J. Chem. Soc.* p. 3164 (1949).
[72] R. A. Abramovitch, *Can. J. Chem.* **38**, 2273 (1960).



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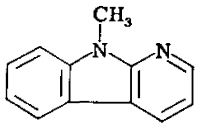
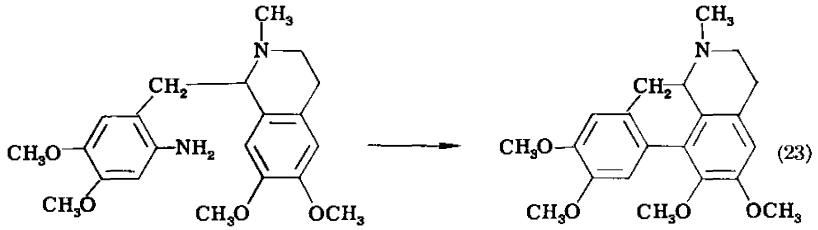


(13)

lytic, the former, involving attack on the very deactivated pyridine ring, should proceed far less readily than the latter, in which attack is on a benzenoid ring. It is also of interest that the yield of (**10**) is greater than that of (**11**), 2-substitution predominating over 4-substitution, as in other radical reactions on pyridine.

Among examples of the use of this method of internuclear cyclization in heterocyclic chemistry is the conversion of diazotized aminolaudanosine (**14**) to 2,3,5,6-tetramethoxyaporphine (**15**), Eq. (**23**).[73]



(14) (15) (23)

An attempt to cyclize the corresponding fully aromatic system (**16**) gave instead the indazole (**17**), Eq. (**24**),[73] probably because the acidity of the bridging methylene group in (**16**) enables cyclization to occur on the diazonium ion through the carbanion.[74]

Centrine[75] and aporphine[76] have been synthesized by cyclizations analogous to that of Eq. (**23**).

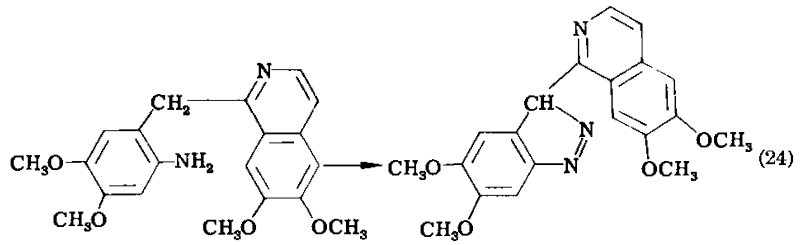
Hey and Osbond converted (**18**) to 5:6-benzoquinoline (**19**) with copper powder in dilute acid solution, reaction probably going through the dihydro compound (**20**) which was oxidized by nitrous acid in the

[73] R. Pschorr, M. Stählin, and M. Silberbach, *Ber. deut. chem. Ges.* **37**, 1926 (1904).

[74] D. F. DeTar, *in* "Organic Reactions" (R. Adams *et al.*, eds.), Vol. 9, p. 424. Wiley, New York, 1957.

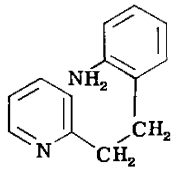
[75] R. D. Haworth, W. H. Perkin, and J. Rankin, *J. Chem. Soc.* p. 2018 (1925).

[76] J. Gadamer, M. Oberlin, and A. Schoeler, *Arch. Pharm.* **263**, 81 (1925).



(16) (17) (24)

reaction medium.[71] It is notable that the cyclization cannot be brought about using the unsaturated compound 2-(*o*-aminostyryl)pyridine, presumably because this has the *trans* configuration of aromatic rings, whereas in many Pschorr reactions a carboxyl group on the ethylenic double bond ensures that the *cis* configuration of the aromatic rings is present.[71]



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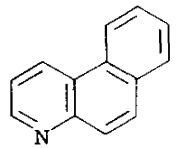

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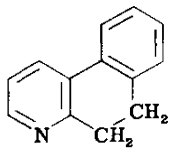

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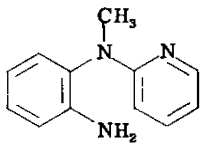

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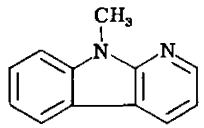

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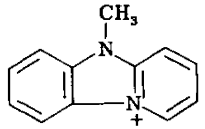


(23) 84%

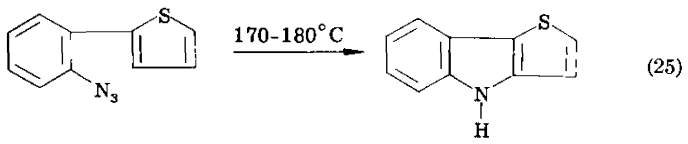
Hey *et al.* also cyclized (**21**) to the α-carboline (**22**) with copper powder; the yield, however, was low, the main product being a salt whose cation was formulated as (**23**) and which was presumably formed by an ionic reaction.[77]

A number of other examples of intramolecular arylations in heterocyclic compounds have been described and reviewed.[74]

Methods for internuclear cyclization other than the Pschorr reaction have been used very little. Hey and Osbond prepared 7,8-di-

[77] R. A. Abramovitch, D. H. Hey, and R. D. Mulley, *J. Chem. Soc.* p. 4263 (1954).

hydro-5,6-benzoquinoline (**20**) by decomposition of the *N*-acetyl-*N*-nitroso derivative of the amine (**18**) in benzene.[71] Smith and Boyer have applied another homolytic method, the thermal decomposition of aryl azides, to effect cyclizations of (**24**) and (**25**), Eqs. (25) and (26), which are analogous to the arylations already described.[78]



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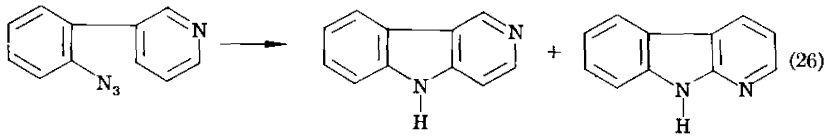


(26)

(25) (94%)

III. Alkylation

A. Sources of Alkyl Radicals

Fewer methods are available for the generation of alkyl than of aryl radicals and a number of these can only be used to produce methyl radicals. Methylation has been, therefore, the most commonly studied alkylation.

1. *Alkyl Radicals from Peroxides*

The thermal decomposition of diacyl peroxides has been the most frequently employed process for the generation of alkyl radicals. The rate and products of the unimolecular decomposition of acetyl peroxide have been the subject of many studies.[79-83] Acetyl peroxide decomposes at a convenient rate at 70–80°C both in the solution and in the gas

[78] P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.* **73**, 2626 (1951).
[79] W. M. Thomas and M. T. O'Shaughnessy, *J. Polymer Sci.* **11**, 455 (1953).
[80] M. Levy, M. Steinberg, and M. Szwarc, *J. Am. Chem. Soc.* **76**, 5978 (1954).
[81] S. D. Ross and M. A. Fineman, *J. Am. Chem. Soc.* **73**, 2176 (1951).
[82] F. G. Edwards and F. R. Mayo, *J. Am. Chem. Soc.* **72**, 1265 (1950).
[83] M. S. Kharasch, J. L. Rowe, and W. H. Urry, *J. Org. Chem.* **16**, 905 (1951).

phase. The acetoxy radicals formed by the initial homolytic fission of the O—O bond undergo decarboxylation more readily than benzoyloxy radicals since the reaction of Eq. (27) is exothermic by

$$CH_3CO_2\cdot \rightarrow CH_3\cdot + CO_2 \qquad (27)$$

17 ± 5 kcal, whereas the analogous decomposition of benzoyloxy radicals is endothermic by 4 kcal, indicating that in the latter radical stabilization must arise from conjugation between the carboxy group and the benzene ring.[84] The average lifetime of the acetoxy radical at 65°C is from 10^{-9} to 10^{-10} sec.[85] The rate of unimolecular decomposition in an inert solvent such as isooctane is 30% slower than in the gas phase,[85] but induced decomposition can be observed when pyridine is used as the solvent.[86]

When the decomposition is carried out in an inert solvent, methyl acetate and ethane are formed, whereas in the gas-phase decomposition methyl acetate is completely absent and ethane is produced in much smaller quantity.[85] It was suggested that the dimers in solution represent the recombination of methyl, and the combination of methyl and acetoxy radicals, within the "solvent cage."[85,87]

The decomposition of diacyl peroxides provides a fairly clean method for the production of alkyl radicals and, therefore, it has been used in most quantitative and preparative studies of the alkylation of heterocyclic compounds.

2. *Electrolytic Method*

Electrolysis of salts of fatty acids gives free radicals which are capable of reacting with added substrates. For instance, when water-free potassium acetate is electrolyzed in the presence of polymerizing substances (e.g., styrene) methyl groups are incorporated as end groups into the polymer.[88] Goldschmidt *et al.*[89] analyzed the products formed in the electrolysis of potassium propionate in propionic acid and showed that they could be accounted for by the following reaction sequence:

[84] L. Jaffe, E. J. Prosen, and M. Szwarc, *J. Chem. Phys.* **27**, 416 (1957); M. Szwarc and L. Herk, *J. Chem. Phys.* **29**, 438 (1958).
[85] L. Herk, M. Feld, and M. Szwarc, *J. Am. Chem. Soc.* **83**, 2998 (1961).
[86] M. Levy and M. Szwarc, *J. Am. Chem. Soc.* **77**, 1949 (1955).
[87] A. Rembaum and M. Szwarc, *J. Am. Chem. Soc.* **77**, 3486 (1955).
[88] S. Goldschmidt and E. Stöckle, *Chem. Ber.* **85**, 630 (1952).
[89] S. Goldschmidt, W. Leicher, and H. Haas, *Ann.* **577**, 153 (1952).

$$\text{R—COOH} \rightarrow \text{RCOO}\cdot \rightarrow \text{R}\cdot \begin{cases} \nearrow \text{dissociation} \\ \rightarrow \text{disproportionation} \\ \searrow \text{reaction with solvent} \end{cases}$$

Reactions of pyridine with a number of alkyl radicals generated by this method have been studied (Section III,B,1).

3. *Decomposition of Lead Tetraacetate*

Thermal decomposition of lead tetraacetate gives rise to methyl radicals, again through the initial formation of acetoxy radicals.[90] An ionic mechanism for the decomposition has also been postulated,[91] and it is possible that both mechanisms may occur, depending on the conditions.

4. *Alkyl Radicals by Hydrogen Abstraction*

Alkyl radicals can be obtained by abstraction of a hydrogen atom from an alkyl group by another radical. This method was utilized for the generation of benzyl radicals from toluene with *tert*-butoxy radical obtained on heating di-*tert*-butyl peroxide.[38] Benzoyl[92] and carboxymethyl[93] radicals have also been obtained by this method. The reaction gives rise to a complex mixture of products and therefore is of rather limited use.

B. Products of Alkylation

1. *Reactions of Methyl and Simple Alkyl Radicals*

Goldschmidt and Minsinger[94] isolated some of the products formed during the decomposition of several diacyl peroxides in pyridine (Table IV). The yields obtained are so far the highest reported for any free-radical alkylation.

The products obtained from the electrolysis of water-free fatty acids in pyridine are similar, although the total yields of alkylated products are considerably lower (Table V),[94] presumably because here the radicals are formed in a high concentration on the anode

[90] M. S. Kharasch, H. N. Friedlander, and W. H. Urry, *J. Org. Chem.* **16**, 533 (1951).
[91] W. A. Mosher and C. L. Kehr, *J. Am. Chem. Soc.* **75**, 3172 (1953).
[92] M. S. Kharasch, D. Schwartz, M. Zimmermann, and W. Nudenberg, *J. Org. Chem.* **18**, 1051 (1953).
[93] M. S. Kharasch and M. T. Gladstone, *J. Am. Chem. Soc.* **65**, 15 (1943).
[94] S. Goldschmidt and M. Minsinger, *Chem. Ber.* **87**, 956 (1954).

and are, therefore, more likely to undergo side reactions (e.g., coupling).

Qualitatively, the results shown in Tables IV and V indicate that the methyl radical, just as the phenyl radical, substitutes pyridine preferentially in the 2- and 4-positions. The absence of the 3-isomer in these reactions is probably a result of the method of analysis

TABLE IV
Alkylation of Pyridine by Peroxides

Peroxide source of radicals	Temp. (°C)	Total yield of Py—R (%)	Ratio of 2-:4-substitution
Diacetyl	100	(R = CH_3) 86.0	7.62 (?)
Dipropionyl	100	(R = C_2H_5) 87.0	2.14
Di-*n*-butyryl	115	(R = C_3H_7) 84.3	2.4
Dilauroyl	115	(R = $C_{11}H_{23}$) 38.4	2.98

(isolation by distillation) during which a small proportion of the 3-isomer may have been lost, since there is evidence that in general the isomer distributions obtained in homolytic methylation are similar to those obtained in phenylation.[95]

TABLE V
Alkylation of Pyridine by Electrolytic Methods

Acid source of radicals	Total yield of Py—R (%)	Ratio of 2-:4-substitution
Acetic	(R = CH_3) 3.5	2.81
Propionic	(R = C_2H_5) 6.85	1.25 (?)
Propionic	(R = C_2H_5) 14.3	2.78
Propionic	(R = C_2H_5) 8.7	1.39
n-Butyric	(R = C_3H_7) 4.38	5.07

2. *Reactions of* $CO_2Me—(CH_2)_n—CH_2\cdot$ *Radicals*

Goldschmidt and Beer have examined the products formed during the thermal decomposition of diacyl peroxides of the type $[CO_2Me—(CH_2)_n—CH_2—COO]_2$, where $n = 1$ and 3, in the presence of a series of organic compounds including pyridine and acridine.[96] The products and yields of the reaction with some aromatic and heterocyclic compounds are shown in Table VI. As expected, acridine and

[95] B. R. Cowley, R. O. C. Norman, and W. A. Waters, *J. Chem. Soc.* p. 1799 (1959).
[96] S. Goldschmidt and L. Beer, *Ann.* **641**, 40 (1961).

anthracene give the 9-substituted products, whereas substitution into the pyridine nucleus again preferentially occurs at the 2-position.

TABLE VI
REACTIONS OF $CO_2Me—(CH_2)_n—CH_2\cdot$ RADICALS

Aromatic compound	n	Reaction product[a]	Yield (mole/mole peroxide)
Anthracene	1	9-R-Anthracene	0.15
		+ anthraquinone	0.02
Pyridine	1	2-R-Py	0.28
		3- and 4-R-Py	0.06
Acridine	1	5-R-Acridine	0.09
Pyridine	3	2-R′-Py	0.28
		3- and 4-R′-Py	0.08

[a] R = $CO_2Me—CH_2CH_2$; R′ = $CO_2Me—(CH_2)_3—CH_2$.

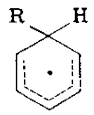
It is instructive to compare the amount of side products (e.g., coupling products of radicals) from the reaction of $CO_2Me—CH_2—CH_2\cdot$ with a number of substrates (Table VII).[96] It may be significant that the proportion of products formed by the coupling of radicals is smallest for anthracene, pyridine, and acridine, indicating the high reactivity of these substrates toward radicals.

TABLE VII
PRODUCTS OF THE DECOMPOSITION OF $[CO_2Me—(CH_2)_2—COO]_2$

Substrate	Temp. (°C)	Yields (mole/mole peroxide)[a] R—H	R′—H	R—R	R—R′	CO_2
Cyclohexane	80	0.41	0.15	0.21	0.25	1.21
n-Heptane	97	0.41	0.12	0.26	0.20	1.22
Anthracene	80	0.33	0.36	0.13	0.09	0.98
Pyridine	100	0.37	0.33	0.10	0.05	1.11
Acridine	80	0.26	0.34	0.11	0.06	0.78

[a] R = $CO_2Me—CH_2—CH_2$; R′ = $CO_2Me—(CH_2)_2—COO$.

It is also interesting that the yield of monomethyl succinate (R′—H), which presumably arises from the abstraction of a hydrogen atom by the acyloxy radical, is higher in the presence of aromatic than aliphatic substrates. This may mean that the acyloxy radical is mainly responsible for the abstraction of a hydrogen atom from the initial adduct (**26**) formed between the alkyl radical and the aromatic substrate (cf. Section II,B).



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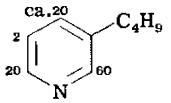


(27)

The most accurate data on isomer distributions in alkylation of heterocycles have been obtained from the reaction of 3-*n*-butylpyridine with methyl radicals in acetic acid.[97] The ratio of the monomethyl products was determined by infrared spectroscopy and gas chromatography and is shown in (**27**). A small amount of 2,6-dimethyl-3-*n*-butylpyridine was also obtained. These ratios again show a high proportion of *ortho* substitution.

The methyl ester of 2-phenyloxazole-4-carboxylate gives the 5-methyl-derivative when methylated with lead tetraacetate.[98]

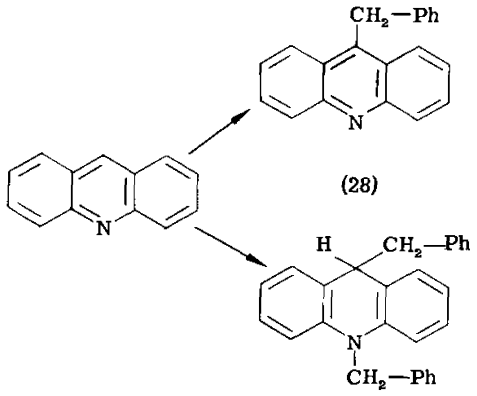
3. *Reactions of Benzyl Radicals*

The first reaction probably involving attack by benzyl radicals on a heterocyclic system was reported by Hickinbottom.[99,100] He found that, when benzyl phenyl ether is heated in quinoline to about 250°C, benzylquinoline and hydroxyphenylquinolines are the main products.

The reaction of benzyl radicals with several heterocyclic compounds was more extensively studied by Waters and Watson,[39,101,102] who generated benzyl radicals by decomposing di-*tert*-butyl peroxide in boiling toluene. The products of the reaction with acridine,[39] 5-phenylacridine,[39] 1:2- and 3:4-benzacridine,[101] and phenazine[102] were studied. Acridine gives a mixture of 9-benzylacridine (17%) (**28**) and 5,10-dibenzylacridan (18%) (**29**) but no biacridan, whereas anthracene gives a mixture of 9,10-dibenzyl-9,10-dihydroanthracene and 9,9′-dibenzyl-9,9′,10,10′-tetrahydrobianthryl. This indicates that initial addition must occur at the *meso*-carbon and not at the nitrogen atom. (Similar conclusions were reached on the basis of methylations discussed in Section III,C.) That this is the position of attack is further supported by the fact that the reaction of benzyl radicals with 5-

[97] E. Hardegger and E. Nikles, *Helv. Chim. Acta* **40**, 2421 (1957).
[98] J. W. Cornforth and E. Cookson, *J. Chem. Soc.* p. 1085 (1952).
[99] W. J. Hickinbottom, *Nature* **142**, 830 (1938).
[100] W. J. Hickinbottom, *Nature* **143**, 520 (1939).
[101] W. A. Waters and D. H. Watson, *J. Chem. Soc.* p. 2082 (1959).
[102] W. A. Waters and D. H. Watson, *J. Chem. Soc.* p. 2085 (1959).

phenylacridine (30) proceeds less easily (40% of phenylacridine was recovered).[39] The products of this reaction are 2.5% of 9,10-dibenzyl-9-phenylacridan (31) and about 10% of 4-benzyl-9-phenylacridine (32), this being the major product. This product is surprisingly not contaminated with other isomers.



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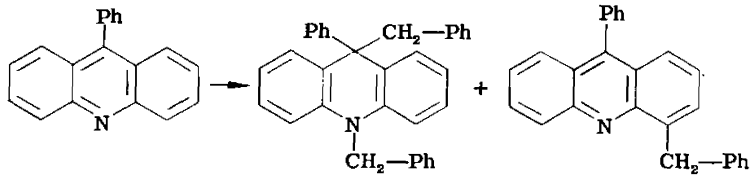
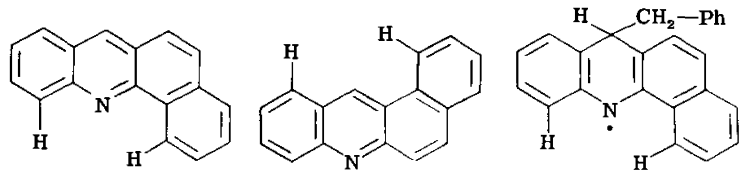
(29)

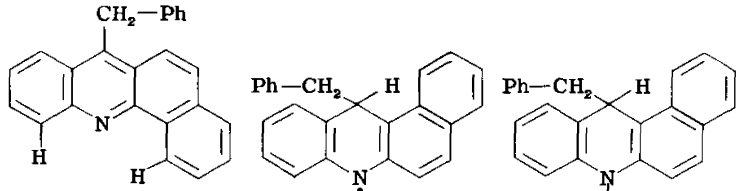


(30) (31) (32)

The conclusion that the initial attack of benzyl radicals on acridine occurs at the *meso*-carbon atom receives further support from the



(33) (34) (35)



(36) (37) (38)

study of benzylation of 3:4- and 1:2-benzacridine, (33) and (34).[101] From the reaction of (33) with benzyl radicals, a 65% yield of 9-benzyl-3:4-benzacridine (36), a small amount of dibenzylbenzacridine, and 30% unchanged starting material are obtained. From the reaction of (34), 75% starting material can be recovered and only 7.5% of 9,10-dibenzyl-1,2-benzacridan (38) is obtained. Both (33) and (34) appear to be less reactive than acridine since more bibenzyl is formed than in the corresponding reaction with acridine. The relatively small amount of reaction of (34) is consistent with the *meso*-carbon being sterically hindered, but the formation of (38) by the addition of a second radical to the initial adduct (37) should be a facile process. On the other hand, the *meso*-carbon of (33) is not sterically hindered, and the adduct (35) is easily formed; its dehydrogenation (by a second benzyl radical) to (36) would occur more easily than the addition of a second benzyl radical to the hindered nitrogen.

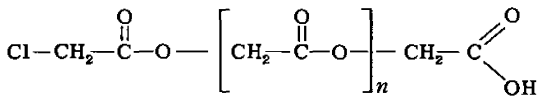
The reaction of benzyl radicals with phenazine gives 5,10-dibenzyl-5,10-dihydrophenazine (39) and 1-benzylphenazine (40) in the approximate ratio of 1:3.[102]

(39) (40)

Only about 1% of bibenzyl is formed during the reaction and it was suggested that this reflects the high reactivity of phenazine toward benzyl radicals. Evidently direct attack on the nitrogen atom occurs with relative ease in this case.

4. *Carboxymethylation*

Free-radical carboxymethylation of several aromatic compounds has been reported,[103] the $\cdot CH_2COOH$ radical being produced by the thermal decomposition of benzoyl peroxide in acetic acid. More recently the carboxymethylation of dibenzofuran brought about by the thermal decomposition of chloroacetylpolyglycolic acid (**41**) has



(**41**)

been studied.[104] The carboxymethyl products are obtained in a high yield (50–60%), and the isomer distribution is the same as that obtained when the reagent is generated from acetic acid by the thermal decomposition of di-*tert*-butyl peroxide (Table VIII). In the

TABLE VIII
CARBOXYMETHYLATION OF DIBENZOFURAN

Radical source	Isomer distribution (%)			
	1-	2-	3-	4-
(**41**)	55	0	15	30
CH_3COOH	51	0	15	34

latter case it is known that free carboxymethyl radicals are formed and, therefore, the similarities of isomer ratios shown in the foregoing indicate a free-radical substitution in the reaction with (**41**). This is the more reasonable since the pattern of the isomer distribution is very different in electrophilic aromatic substitution, and the foregoing results are in qualitative agreement with the theory for free-radical reactions. The free-radical localization energies calculated by the simple Hückel method are[104]: 1-, 2.38β; 2-, 2.53β; 3-, 2.48β; 4-, 2.44β.

[103] M. T. Gladstone, *J. Am. Chem. Soc.* **76**, 1581 (1954).
[104] P. L. Southwick, M. W. Munsell, and E. A. Bartkus, *J. Am. Chem. Soc.* **83**, 1358 (1961).

C. RATES OF ALKYLATIONS

Most quantitative studies concern methylation and were carried out by Szwarc and his collaborators.

The competitive method employed for determining relative rates of substitution in homolytic phenylation cannot be applied for methylation because of the high reactivity of the primary reaction products toward free methyl radicals. Szwarc and his co-workers, however, developed a technique for measuring the relative rates of addition of methyl radicals to aromatic and heteroaromatic systems.[86,105] In the decomposition of acetyl peroxide in isooctane the most important reaction is the formation of methane by the abstraction of hydrogen atoms from the solvent by methyl radicals. When an aromatic compound is added to this system it competes with the solvent for methyl radicals, Eqs. (28) and (29). Reaction (28) results in a decrease in the amount

$$CH_3\cdot + C_8H_{18} \xrightarrow{k_1} CH_4 + C_8H_{17}\cdot \qquad (28)$$

$$CH_3\cdot + Ar{-}H \xrightarrow{k_2} Ar(H)CH_3 \quad \text{(initial adduct)} \qquad (29)$$

of methane formed, and the relative magnitudes of the rate constants k_1 and k_2 can be calculated from the analysis of the gaseous products. (The other gaseous products are carbon dioxide, formed by decarboxylation of the acetoxy radical, and a small amount of ethane formed by dimerization of methyl radicals.) The accuracy of this method depends on the validity of several assumptions: (*a*) that methyl radicals are only consumed in reactions (28) and (29) and in their combination within a solvent cage to form ethane and methyl acetate; (*b*) that methane is only formed by reaction (28); and (*c*) that the only reagent present capable of initiating a reaction with the aromatic compound is the methyl radical. It is probable, in fact, that none of these conditions is strictly obeyed, but nevertheless, under the experimental conditions used by Szwarc and his collaborators, i.e., a dilute solution containing a very small amount of acetyl peroxide and a large excess of aromatic compound, the errors caused by side reactions are reduced to a minimum. In support of the assumptions Szwarc *et al.*[106] have shown that the ratio k_1/k_2 remains constant when

[105] M. Levy and M. Szwarc, *J. Am. Chem. Soc.* **76**, 5981 (1954).

the concentration of aromatic substrate is varied by a factor of 4, and that a change in temperature from 65 to 85°C causes very little change in this ratio whereas there is a tenfold increase in the rate of unimolecular decomposition of acetyl peroxide. Evidently the stationary concentration of methyl radicals does not affect k_1/k_2.

Szwarc and his co-workers have measured the methyl affinities (that is, reactivities toward methyl radicals compared with that of benzene) of a number of heterocyclic compounds. These, together with the methyl affinities of some homocyclic compounds, are set out in Table IX.

TABLE IX
THE METHYL AFFINITIES OF AROMATICS[106]

Aromatic compound	Methyl affinity
Benzene	1
Pyridine	3
Pyrazine	ca. 18
Naphthalene	22
Quinoline	29
Isoquinoline	36
Anthracene	820
Acridine	430
Phenazine	ca. 250

It is notable that pyridine is activated relative to benzene and quinoline is activated relative to naphthalene, but that the reactivities of anthracene, acridine, and phenazine decrease in that order. A small activation of pyridine and quinoline is reasonable on the basis of quantum-mechanical predictions of atom localization energies,[107] whereas the unexpected decrease in reactivity from anthracene to phenazine can be best interpreted on the basis of a model for the transition state of methylation suggested by Szwarc and Binks.[106] The coulombic repulsion between the π-electrons of the aromatic nucleus and the p-electron of the radical should be smaller if the radical approaches the aromatic system along the nodal plane rather than perpendicular to it. This approach to a nitrogen center would be very unfavorable, however, since the lone pair of electrons of the nitrogen lies in the nodal plane and since the methyl radical is

[106] M. Szwarc and J. H. Binks, "Theoretical Organic Chemistry," p. 262. Butterworths, London, 1959.
[107] C. A. Coulson, *J. Chem. Soc.* p. 1435 (1955).

slightly nucleophilic.[95] Since acridine is about half as reactive as anthracene, the attack of a methyl radical on a nitrogen atom must be very slow compared with the rate of its reaction on carbon. The presence of two nitrogen atoms in phenazine is thought to activate the remaining positions, and, therefore, the decrease in reactivity from acridine to phenazine is less than twofold.[106]

This interpretation for acridine is consistent with the finding of Waters and Watson[39] that benzyl radicals attack the *meso*-carbon but not nitrogen, but it is possible that methyl radicals, like benzyl radicals, also react at the nitrogen centers of phenazine (cf. Section III,B,3).

Affinities toward other alkyl radicals have also been measured by Szwarc and his co-workers using techniques similar to those described above.[106] It is interesting to compare the affinities of naphthalene with those of quinoline toward methyl, ethyl, and n-propyl radicals (Table X).

TABLE X
RADICAL AFFINITIES OF NAPHTHALENE AND QUINOLINE

Compound	Propyl affinity	Ethyl affinity	Methyl affinity
Naphthalene	34.2	34.5	30
Quinoline	73	63	46

On the basis of the reaction of alkyl radicals with a number of polycyclic aromatics, Szwarc and Binks calculated the "relative selectivities" of several radicals[106]: methyl, 1 (by definition); ethyl, 1.0; n-propyl, 1.0; trichloromethyl, 1.8. The relative reactivities of the three alkyl radicals toward aromatics therefore appears to be the same. On the other hand, quinoline (the only heterocyclic compound so far examined in reactions with alkyl radicals other than methyl) shows a steady increase in its reactivity toward methyl, ethyl, and n-propyl radicals. This would suggest that the nucleophilic character of the alkyl radicals increases in the order: Me < Et < n-Pr, and that the selectivity of the radical as defined by Szwarc is not necessarily a measure of its polar character.

IV. Hydroxylation

Free-radical hydroxylation of heterocyclic compounds has almost always been studied in the context of the relation of chemical hy-

droxylations to biological processes. When an aromatic compound "foreign" to the organism is administered to animals it is usually converted to its hydroxy derivatives and excreted as such or as their "conjugates" with, e.g., glucuronic acid. These *in vivo* hydroxylations generally result in a fairly random distribution of the hydroxy isomers.[108] Similarly, nonspecific hydroxylation is brought about by an enzyme system in liver microsomes.[109] In order to elucidate the mechanism of hydroxylation in the biological processes two simple chemical systems have been considered as models for such reactions: Fenton's reagent (ferrous ion and hydrogen peroxide); and a system consisting of ferrous ion, EDTA, ascorbic acid, and oxygen.

A. Fenton's Reagent

The most commonly employed reagent for the hydroxylation of aromatic compounds is that consisting of ferrous ion and hydrogen peroxide. The suggestion that hydroxyl radicals are intermediates in this reaction was first made by Haber and Weiss, who proposed the following radical-chain mechanism for the process[110]:

$$Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + OH^- + \cdot OH \quad (30)$$

$$\cdot OH + Fe^{++} \rightarrow OH^- + Fe^{+++} \quad (31)$$

$$\cdot OH + H_2O_2 \rightarrow H_2O + \cdot O_2H \quad (32)$$

$$\cdot O_2H + H_2O_2 \rightarrow O_2 + H_2O + \cdot OH \quad (33)$$

Although alternative ionic mechanisms have been formulated,[111] the essential feature of the reaction, namely the generation of free hydroxyl radicals, is now generally accepted.[112]

1. *Mechanism of Hydroxylation*

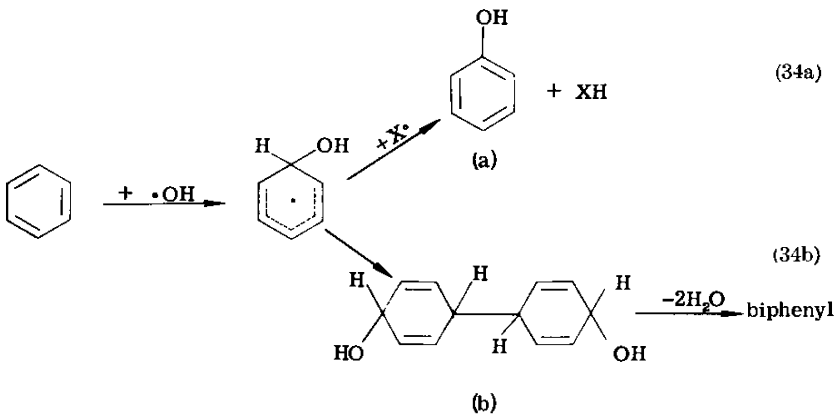
The mechanism of hydroxylation of heterocyclic compound has not been studied, but the mechanistic aspects of hydroxylation of homocyclic compounds may again serve as a basis for discussion.

[108] R. T. Williams, "Detoxication Mechanisms," Chapters 7 to 14. Chapman and Hall, London, 1959.
[109] C. Mitoma, H. S. Posner, H. C. Reitz, and S. Udenfriend, *Arch. Biochem. Biophys.* **61**, 431 (1956).
[110] F. Haber and J. Weiss, *Proc. Roy. Soc.* (*London*) **A147**, 332 (1934).
[111] W. C. Bray and M. H. Gorin, *J. Am. Chem. Soc.* **54**, 2124 (1932); A. E. Cahill and H. Taube, *J. Am. Chem. Soc.* **74**, 2312 (1952).
[112] G. H. Williams, "Homolytic Aromatic Substitution," p. 110. Pergamon Press, London, 1960.

The first problem is the nature of the hydroxylating species responsible for the reaction of the aromatic substrate. According to the Haber-Weiss mechanism this may be the hydroxyl ($\cdot OH$) or perhydroxyl ($\cdot O_2H$) radical. The isomer distributions obtained in the hydroxylation of nitrobenzene[113] and chlorobenzene[114] by Fenton's reagent are similar to those obtained when the attacking radicals are generated by the action of X-rays on water. Since perhydroxyl radicals do not participate in the latter reaction, it is reasonable to conclude that hydroxyl radicals are also responsible for the reaction with Fenton's reagent. Recently more accurate data have been obtained for the hydroxylation of anisole and fluorobenzene with Fenton's reagent and with hydrogen peroxide and ultraviolet light.[115] The isomer distributions given by the two reagents are the same within the limits of the experimental error, in support of the idea that the hydroxyl radical is the species responsible for the reaction. The relative rates of substitution of several monosubstituted benzenoid compounds by the free hydroxyl radical show the same order of reactivities as is found in electrophilic aromatic substitution but a different order from that of other free-radical aromatic substitutions. It can be concluded that the free hydroxyl radical, just as chlorine and bromine atoms, is strongly electrophilic.[115] This is consistent with the distribution of isomers obtained in hydroxylations: for example, anisole is substituted almost entirely in the *ortho* and *para* positions, whereas nitrobenzene gives rise to a large proportion of the *meta*-hydroxy isomer.[115]

The attack on the aromatic nucleus by hydroxyl radicals is probably analogous to that by phenyl and methyl radicals, Eq. (34a,b). Evidence that the first step is the addition of hydroxyl radical to benzene, rather than abstraction of a hydrogen atom, has recently been adduced from a study of the radiolysis of water–benzene mixtures.[116] The familiar addition complex may undergo two reactions to form the phenolic and dimeric products respectively, Eq. (34a,b). Alternative mechanisms for the formation of the dimer have been formulated, but in view of the lack of experimental evidence for any of the mechanisms further discussion of this problem is not justified.

[113] H. Loebl, G. Stein, and J. Weiss, *J. Chem. Soc.* p. 2074 (1949); *ibid.* p. 2704 (1950).
[114] G. R. A. Johnson, G. Stein, and J. Weiss, *J. Chem. Soc.* p. 3275 (1951).
[115] R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc.* p. 138 (1962).
[116] L. M. Dorfman, R. E. Bühler, and I. A. Taub, *J. Chem. Phys.* **36**, 549 (1962).



2. *Products of Hydroxylation of Heterocycles*

Heterocyclic compounds have in most cases been hydroxylated by modified forms of Fenton's reagent. For instance, EDTA[117] or pyrophosphate[118] have been added to the system to complex the ferrous ions. It has been shown in the reactions of benzenoid compounds, however, that addition of complexing agents does not affect the distribution of isomers obtained by Fenton's reagent,[115] and therefore the hydroxyl radical must still be the hydroxylating species.

The products obtained in the hydroxylation of heterocyclic compounds are set out in Table XI.

The yield of hydroxylated products is always very low, and there are usually a number of by-products. For instance, side chains of aromatic nuclei are easily attacked, as shown by the formation of 5-hydroxymethyluracil from thymine.[121] Breslow and Lukens[117] measured both the amount of 3-hydroxyquinoline formed and the quinoline consumed during hydroxylation with Fenton's reagent and EDTA in the presence of several adducts (Table XII).

[117] R. Breslow and L. N. Lukens, *J. Biol. Chem.* **235**, 292 (1960).
[118] C. Nofre, A. Lefier, and A. Cier, *Compt. rend. acad. sci.* **253**, 687 (1961).
[119] C. Nofre, A. Cier, C. Michou-Saucet, and J. Parnet, *Compt. rend. acad. sci.* **251**, 811 (1960).
[120] J. A. R. Mead, J. N. Smith, and R. T. Williams, *Biochem. J.* **68**, 67 (1958).
[121] A. Cier, A. Lefier, M. Ravier, and C. Nofre, *Compt. rend. acad. sci.* **254**, 504 (1962).

TABLE XI
PRODUCTS OF HYDROXYLATION OF HETEROCYCLES BY FENTON'S REAGENT[a]

Aromatic compound	Complexing agent	Products	Ref.
Purine	Pyrophosphate	6- + 8-Hydroxy	118
6-Hydroxypurine	Pyrophosphate	6,8-Dihydroxy	118
2,6-Dihydroxypurine	Pyrophosphate	Uric acid	118
Adenine	Pyrophosphate	8-Hydroxy	118
2-Aminopurine	Pyrophosphate	Guanine	118
Tryptophan	Pyrophosphate	5-Hydroxy and a compound possibly 7-hydroxy	119
Kynurenine	Pyrophosphate	3- and 5-Hydroxy + kynurenic and xanthurenic acid	119
β-Indoleacetic acid	Pyrophosphate	5-Hydroxy	119
Coumarin	None	3-, 5-, 7-, 8-(trace), and 6-Hydroxy (trace) but no 4-hydroxy	120
Quinoline	EDTA	Only 3-hydroxy detected	117
Pyrimidine-2,4-dione (uracil)	EDTA	Isobarbituric acid, 6.5%	121
4-Aminopyrimidine-2-one (cytosine)	EDTA	5-Hydroxy, 4.7%	121
5-Methyluracil (thymine)	EDTA	5-Hydroxymethyl uracil, 0.7%	121
5-Methylcytosine	EDTA	5-Hydroxymethyl cytosine, 0.6%	121

[a] Reactions were carried out at 37°C and pH 6.8–7.2.

The yield of 3-hydroxyquinoline relative to the amount of quinoline consumed is low but is increased markedly by the presence of ascorbic acid. This was attributed to the regeneration of ferrous ions by reduction of the ferric ion formed in the first step of the reaction.

TABLE XII
THE HYDROXYLATION OF QUINOLINE

Addition	Quinoline utilized (moles/ml)	3-Hydroxyquinoline formed (moles/ml)
None	3.1	0.03
Ascorbic acid	15.3	0.64
Dehydroascorbic acid	3.1	0.04
Ascorbic + dehydroascorbic acids	15.3	0.52

B. Hydroxylation by Ferrous Ion–Oxygen–Ascorbic Acid

1. *The Products of the Reaction*

Udenfriend *et al.* observed that aromatic compounds are hydroxylated by a system consisting of ferrous ion, EDTA, ascorbic acid, and oxygen.[122] Aromatic and heteroaromatic compounds are hydroxylated at the positions which are normally most reactive in electrophilic substitutions. For example, acetanilide gives rise exclusively to the *o*- and *p*-hydroxy isomers whereas quinoline gives the 3-hydroxy product.[122a] The products of the reaction of this system with heterocyclic compounds are shown in Table XIII.

TABLE XIII
Products of Hydroxylation of Heterocycles by Udenfriend's System

Aromatic compound	Positions of substitution (and relative amounts of isomers where quoted)	Ref.
Coumarin	5 and 7 (and 6, trace)	120
Flavone	4′(54.0); 3′(40.5); 6(3.4); 7(1.4)	123
6-Hydroxyflavone	4′(57.1); 3′(42.9)	123
7-Hydroxyflavone	4′(64.5); 3′(35.5)	123
5,7-Dihydroxyflavone	4′(60.0); 3′(40.0)	123
4′-Hydroxyflavone	3′(85.8); 6(12.9); 7(1.3)	123
Indole-3-carboxylic acid	5 and 7	124
Kynurenine	3 and 5	124
Quinoline	Mainly 3	117, 122
Tryptophan	5 and 7	124

It is notable that flavone and its derivatives are substituted predominantly in the phenyl group at positions 3′ and 4′ whereas reaction with Fenton's reagent gives mainly the 3-hydroxy isomer.[123] Similarly, comparison of the distribution of products from coumarin obtained with Udenfriend's system with that given by Fenton's reagent reveals some differences between the two systems. These differences were not always recognized and have been questioned,[117] but a recent study has shown that there are differences in the distribution of isomers (well outside the experimental error) when monosubstituted benzenoid compounds are hydroxylated by the two systems.[115]

[123] B. B. Brodie, J. Axelrod, P. A. Shore, and S. Udenfriend, *J. Biol. Chem.* **208**, 741 (1954).

[122a] In less acidic media, quinoline is substituted by electrophilic reagents predominantly at the 3-position, although the reason for this is not clear; see P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution," p. 198. Butterworths, London, 1959.

[123] B. Winicki, J. Chopin, A. Cier, and C. Nofre, *Bull. soc. chim. biol.* **42**, 1097 (1960).

[124] C. E. Dalgliesh, *Arch. Biochem. Biophys.* **58**, 214 (1955).

2. *The Mechanism of the Reaction*

The mechanism of hydroxylation by Udenfriend's system is not yet clear. It is known that atmospheric oxygen is incorporated into the phenolic group[125] and that ascorbic acid cannot be replaced by dehydroascorbic acid or diketones[117] as was thought earlier.[126] On the other hand, very little is known about the nature of the hydroxylating species. Udenfriend *et al.* argued that the isomer distribution is not as random as that resulting from free-radical substitutions and that the reagent is electrophilic and is possibly the hydroxyl cation (OH^+).[126,127] Dalgliesh later suggested that free radicals are involved since they can attack electronegative sites.[124] Mason preferred the iron–oxygen complex FeO^{++} as the hydroxylating species,[128] but on the basis of later work suggested that a free-radical mechanism is more likely.[129] The suggestion that the hydroxyl radical is involved,[117] as it is in hydroxylation by Fenton's reagent, is rendered unlikely by the finding that the product distributions from the two processes are quite different.[115]

3. *Comparison with Biological Hydroxylations*

The distributions of phenolic isomers in hydroxylations in the animal body are often similar to those obtained by Fenton's reagent. For example, the hydroxylation of coumarin by the rabbit gives the six hydroxycoumarins in amounts decreasing in the order[130]: 3- >7- >6- >8- >4- ~5-, whereas Fenton's reagent gives mainly the 3-, 5-, and 7-derivatives with traces of the 6- and 8-derivatives.[120] It may, however, be misleading to draw conclusions about the nature of

[125] H. S. Mason and I. Onoprvenko, *Federation Proc.* **15**, 310 (1956).

[126] S. Udenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie, *J. Biol. Chem.* **208**, 731 (1954).

[127] S. Udenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie, *Federation Proc.* **11**, 300 (1952).

[128] H. S. Mason, *in* "Advances in Enzymology" (F. F. Nord, ed.), Vol. 19, p. 135. Interscience, New York, 1957.

[129] D. R. Buhler and H. S. Mason, *Arch. Biochem. Biophys.* **92**, 424 (1961).

[130] M. Kaighen and R. T. Williams, *J. Med. Pharm. Chem.* **3**, 25 (1961).

the hydroxylating species in the animal from such comparisons, for the metabolite pattern is dependent on the species.[120,131]

Hydroxylation has been effected by incubating liver microsomes with aromatic compounds in the presence of reduced triphosphopyridine nucleotide and oxygen.[109] For instance, quinoline gives mainly the 3-hydroxy derivative, together with traces of the 6- and 7-isomers.[109] The phenolic oxygen has been shown to be derived from atmospheric oxygen,[132] and in this respect Udenfriend's system would appear to be a better model than Fenton's reagent for the biological process.

V. Halogenation

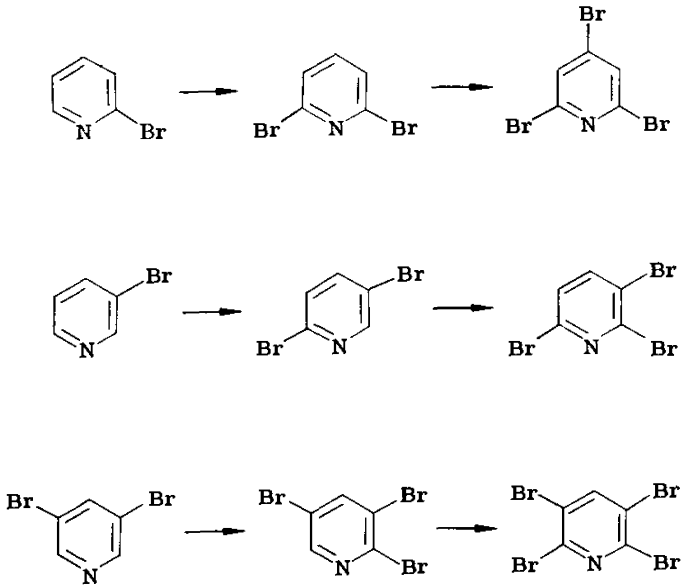
Gas-phase halogenation of benzenoid and heterocyclic compounds has been extensively studied by Wibaut and his co-workers, and a review of this work is available.[133]

The reactions were carried out at a temperature range of 200–500°C in a vessel packed with pumice or graphite as a contact substance. The most striking result of these investigations is that a change in the orientation of the halogen atom takes place as the temperature is raised. This feature of the reaction is illustrated in Table XIV. Bromination of several mono-, di-, and tri-substituted pyridines at 500°C gives the products[139] shown in Scheme 2. The

TABLE XIV
HALOGENATION OF HETEROCYCLES

Aromatic compound	Halogen	Temp. (°C)	Substitution products	Ref.
Pyridine	Br_2	300	3- and 3,5-	134
	Br_2	500	2- and 2,6-	134
	Cl_2	220	3- and 3,5-	135
	Cl_2	270–400	2- and 2,6-	135
Quinoline	Br_2	300	3-	136
	Br_2	450–500	2- and a little 3-	136
Isoquinoline	Br_2		1-	136
Thiazole	Br_2	250 and 450	2-	136
Benzothiazole	Br_2		2-	136
2,2′-Bipyridyl	Br_2	500	6- and 6,6′-	138
2,2′,2″-Tripyridyl	Br_2	500	6′- and 6′,6″-	138
Thiophene	Br_2	750	3-	137
	Br_2	below 750	2-	137
	Cl_2	200	2-	137
		550	2-, ($\frac{3}{4}$) and 3-, ($\frac{1}{4}$)	137
		600	2-, ($\frac{1}{4}$) and 3-, ($\frac{3}{4}$)	137

[131] D. V. Parke and R. T. Williams, *Biochem. J.* **63**, 12P (1956).
[132] O. Hayaishi, S. Rothberg, and A. H. Mehler, *130th Meeting, Am. Chem. Soc., Atlantic City, N. J., 1956*, p. 53c.
[133] J. P. Wibaut, *Experientia* **5**, 337 (1949).



SCHEME 2

rate of bromination decreases when bromine atoms are substituted into the aromatic ring.

The change in orientation was attributed to the occurrence of two mechanisms, a polar reaction occurring at lower temperatures on the surface of the vessel, and a radical reaction occurring at higher temperatures.[133]

The work of Wibaut's school was more recently extended by den

[134] H. J. den Hertog and J. P. Wibaut, *Rec. trav. chim.* **51**, 381 (1932).
[135] J. P. Wibaut and J. R. Nicolaï, *Rec. trav. chim.* **58**, 709 (1939).
[136] H. E. Jansen and J. P. Wibaut, *Rec. trav. chim.* **56**, 699 (1937).
[137] C. D. Hurd and H. J. Anderson, *J. Am. Chem. Soc.* **75**, 3517 (1953).
[138] F. H. Burstall, *J. Chem. Soc.* p. 1662 (1938).
[139] H. J. den Hertog and J. P. Wibaut, *Rec. trav. chim.* **51**, 940 (1932).

Hertog *et al.*[140] who investigated the bromination of 2,6-dibromopyridine in pumice-packed reactors. The products of the reaction at a series of temperatures are shown in Table XV.

TABLE XV
BROMINATION OF 2,6-DIBROMOPYRIDINE

Temp. (°C)	Yield (%)		
	2,4,6-Tribromo-	2,3,4,6-Tetrabromo-	Pentabromo-
455	3	—	—
485	16–17	0.5	—
500	22–23	1	—
515	28–29	1–2	—
530	35–36	3–4	0.5

Bromination at 450°C hardly occurs, but when the pumice is impregnated with ferrous or cuprous bromide a much better yield of 2,4,6-tribromopyridine is obtained. When pyridine is brominated at 180°C in the presence or absence of impregnated pumice only 2-bromo- and 2,6-dibromopyridine are formed. These facts are not consistent with an electrophilic substitution, which should take place at the 3-position. On the other hand, the high temperature coefficient of the reaction (cf. Table XV) and the fact that ultraviolet light has no effect on the reaction argue against a simple free-radical substitution.[140]

Recent work by Engelsma and Kooyman[141] shows that in the gas-phase halogenation of several monosubstituted benzenoid compounds a novel pattern of substitution is obtained. Groups *ortho* and *para* directing in electrophilic substitution become mainly *meta* directing, whereas substituents such as the cyano group direct substitution mainly into the *para* position. Some evidence was obtained that the reaction involves addition of a halogen atom to the aromatic nucleus, Eq. (35), followed by ion-pair formation, Eq. (36). The ion-pair collapses to an aryl radical and hydrogen halide, Eq. (37), and the aryl radical reacts with a molecule of halogen to form aryl halide and a halogen atom, Eq. (38). The observed isomer ratios are consistent with this mechanism.[142]

[140] H. J. den Hertog, W. P. Combé, and C. R. Kolder, *Rec. trav. chim.* **77**, 66 (1958).
[141] J. W. Engelsma and E. C. Kooyman, *Rec. trav. chim.* **80**, 526, 537 (1961).
[142] J. W. Engelsma, Thesis, Leiden, 1960.

$$ArH + X\cdot \rightleftharpoons \dot{Ar}\begin{matrix}H\\X\end{matrix} \quad (35)$$

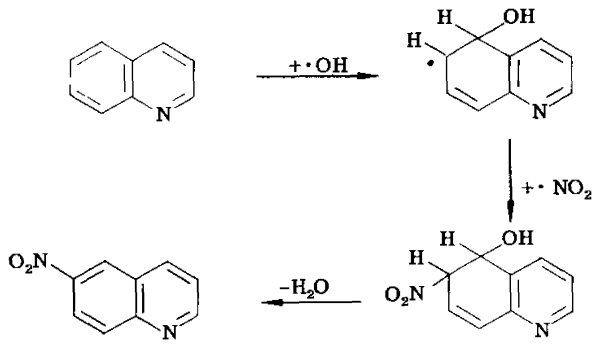
$$\dot{Ar}\begin{matrix}H\\X\end{matrix} \rightleftharpoons (Ar^+—H\ X^-) \quad (36)$$

$$(Ar^+—H\ X^-) \rightarrow Ar\cdot + HX \quad (37)$$

$$Ar\cdot + X_2 \rightarrow Ar—X + X\cdot \quad (38)$$

VI. Other Reactions

Den Hertog and Overhoff[143] observed that when pyridine in sulfuric acid is added to molten potassium sodium nitrate the 3-nitro derivative is formed at 300°C, whereas at 450°C 2-nitropyridine is the main product. The latter is probably a free-radical process. Schorigin and Toptschiew[144] obtained 7-nitroquinoline by the action of nitrogen peroxide on quinoline at 100°C, possibly through the homolytic addition of $NO_2\cdot$. Laville and Waters[145] reported that during the decomposition of pernitrous acid in aqueous acetic acid, quinoline is nitrated in the 6- and 7-positions. They considered that the reaction proceeds as shown in Scheme 3.

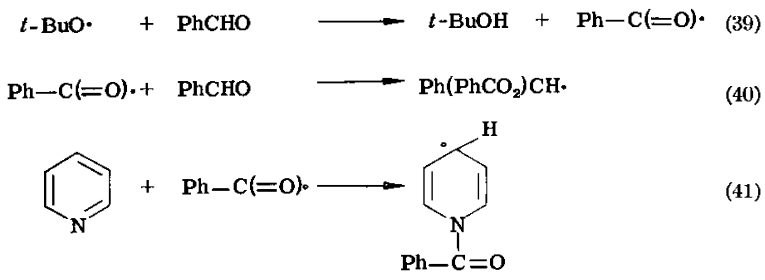


SCHEME 3

Kharasch *et al.*[92] proposed the mechanism shown in Eqs. (39) to (42) to account for the formation of 4-(α-benzoxybenzyl)pyridine

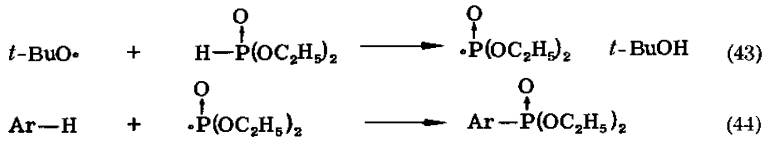
[143] H. J. den Hertog and J. Overhoff, *Rec. trav. chim.* **49**, 552 (1930).
[144] P. Schorigin and A. Toptschiew, *Ber. deut. chem. Ges.* **69**, 1874 (1936).
[145] J. R. Laville and W. A. Waters, *J. Chem. Soc.* p. 400 (1954).

(42) from the reaction of di-*tert*-butyl peroxide and benzaldehyde with pyridine.



(42)

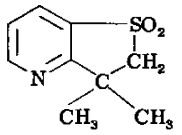
The decomposition of di-*tert*-butyl peroxide in the presence of diethyl phosphite and an aromatic substrate leads to free-radical phosphination, Eqs. (43) and (44).



Dibenzofuran and carbazole gave yields of 69 and 80%, respectively, of the phosphinated derivative, but the position of substitution was not determined.[146]

[146] E. F. Jason and A. K. Fields, *J. Org. Chem.* **27**, 1402 (1962).

The reaction of 2,6-di-*tert*-butylpyridine with SO_3 at elevated temperatures gives (43) in addition to the 3-sulfonic acid.[147]



(43)

The intramolecular attack on the alkyl side chain is suggestive of a free-radical process.

VII. Theoretical Treatments

The free valence number,[148] which can be regarded as a measure of the residual bonding power of an atom, was the first theoretical index used to correlate the reactivities of aromatic compounds toward free radicals. Kooyman and Farenhorst noted a very good correlation between F_{max} and the relative reactivities of aromatic hydrocarbons toward the trichloromethyl radical.[149] They pointed out, however, that the free valence number applies to the stationary state of the free molecule, i.e., it is a static property, and might give information only on the first stages of the reaction. That it gives satisfactory correlations could depend on the fact that a certain trend in the early stages of the process could prevail also in later stages, at least when reactions involving carbon atoms of the same bonding type are being compared.

A second theoretical index, and one for which there appears to be more justification in its application to free-radical reactions, is the atom localization energy. This index is a measure of the energy required to localize one electron of the π-electron system in the aromatic molecule at the point of attack of the radical.[150] The formation of the intermediate adduct in a free-radical aromatic substitution may be regarded as the sum of two processes: one, the localization of an electron at the point of attack; and the other, the pairing of this

[147] H. C. van der Plas and T. H. Crawford, *J. Org. Chem.* **26**, 2611 (1961).
[148] C. A. Coulson, *Trans. Faraday Soc.* **42**, 265 (1946).
[149] E. C. Kooyman and E. Farenhorst, *Nature* **169**, 153 (1952).
[150] G. W. Wheland, *J. Am. Chem. Soc.* **64**, 900 (1942).

electron with that on the attacking radical. The energy change in the latter step would be independent of the nature of the aromatic nucleus (where carbon atoms of the same bonding type are involved) and constant for a particular attacking radical. The energy of formation of the intermediate is, therefore, related to the atom localization energy. A correlation between the reactivities of aromatic carbon atoms toward a radical and their atom localization energies would imply a relationship between the enthalpy of formation of the intermediate and the enthalpy of activation of this process. Such a correlation has been noted by Szwarc and Binks for the methyl affinities of monocyclic and polycyclic aromatic compounds.[106]

It is difficult to treat the effect of a heteroatom on the localization energies of aromatic systems, but Brown[151] has derived molecular orbital parameters from which he has shown that the rates of attack of the phenyl radical at the three positions of pyridine relatively to benzene agree within 10% with the experimental results. He and his co-workers have shown that the formation of 1-bromoisoquinoline on free-radical bromination of isoquinoline is in agreement with predictions from localization energies for physically reasonable values of the Coulomb parameters,[152] but the observed orientation of the phenylation of quinoline cannot be correlated with localization energies.[153]

Brown has also predicted, from localization energy calculations, that pyrrole and glyoxaline should react with radicals mainly at the 2-position, whereas pyrazole should be most reactive at the 3-position.[154] Brown and Heffernan's calculation[155] that the orientation in pyrimidine substitution should be $4 > 2 > 5$ is in agreement with the results from the *p*-nitrophenylation of pyrimidine.[12]

It is of interest that both the methyl affinities[106] and the reactivities of aromatic compounds toward the phenyl radical[156] are correlated both by F_{max} and by atom localization energies. Dewar[157] has shown that the energy required to remove one atom from conjugation (in a hydrocarbon containing an even number of carbon atoms) is greater

[151] R. D. Brown, *J. Chem. Soc.* p. 272 (1956).
[152] R. D. Brown and R. D. Harcourt, *Tetrahedron* **8**, 23 (1960).
[153] R. D. Brown and R. D. Harcourt, *J. Chem. Soc.* p. 3451 (1959).
[154] R. D. Brown, *Australian J. Chem.* **8**, 100 (1955).
[155] R. D. Brown and M. L. Heffernan, *Australian J. Chem.* **9**, 83 (1956).
[156] D. R. Augood, D. H. Hey, and G. H. Williams, *J. Chem. Soc.* p. 44 (1953); D. H. Hey and G. H. Williams, *Discussions Faraday Soc.* **14**, 216 (1953).
[157] M. J. S. Dewar, *J. Am. Chem. Soc.* **74**, 3355 (1952).

the smaller its free valence number, so that the fact that both F_{max} and atom localization energies correlate radical reactivities is comprehensible. He has argued that the success of the free valence method in predicting radical reactivities rests on this relation between F_{max} and atom localization energies, but provides no evidence for the basic premises of this method.

The Action of Metal Catalysts on Pyridines

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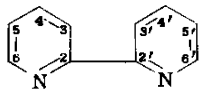
I. Introduction

In 1956 it was found[1] that when pyridine is refluxed with a modified Raney-nickel catalyst, 2,2′-bipyridine (**1**) is formed in satisfactory yield. The isomeric bipyridines could not be detected, and the product was readily purified. Similar heterocyclic biaryls have been formed in the same way from substituted pyridines and from some related compounds, the yield being dependent on the nature of the compound. The reaction has become the method of choice for the preparation of 2,2′-bipyridine, and it is now used on an industrial scale. Bipyridyls are of particular importance as chelating agents.



(1)

Several "side reactions" have also been observed, and, for the present purpose, all reactions leading to products other than 2,2′-bipyridines will be considered under this heading. Some of these undoubtedly involve hydrogen derived from the catalyst, but no attempt will be made adequately to review the field of reactions involving pyridines, metal catalysts, *and* hydrogen.

[1] G. M. Badger and W. H. F. Sasse, *J. Chem. Soc.* p. 616 (1956).

2,2′-Bipyridines have also been prepared from substituted pyridines by methods which are based on the action of metal catalysts on suitable functional groups attached to the pyridine nucleus. 2,2′-Bipyridine itself has been prepared by the action of copper[2] or of Raney nickel[3] on 2-halogenated pyridines. Similarly, 9-chloroacridine reacts with copper[4] or Raney nickel[5] to give 9,9′-biacridine. Other examples include the formation of 2,2′-biquinoline during the decarboxylation of quinaldinic acid[6] and during the desulfurization of 2-mercaptoquinoline by means of Raney cobalt.[7] As all these reactions depend on the nature of the functional groups and can also be observed with compounds other than azahydrocarbons, transformations of this type will not be included.

II. The Formation of 2,2′-Biaryls

A. The Formation of 2,2′-Bipyridine from Pyridine

1. *Catalysts Other Than Raney Catalysts*

The formation of trace amounts of 2,2′-bipyridine following reaction between pyridine and ammonia in the presence of a variety of catalysts[8] led Wibaut and Willink[9] to develop a method for the preparation of 2,2′-bipyridine from pyridine under the influence of a nickel-alumina catalyst. Using a pyridine-to-catalyst ratio of 10:1, temperatures between 320° and 325°C, and pressures between 42 and 44 atm, 2,2′-bipyridine was formed in yields of 0.30–0.67 gm per gram of catalyst. This method was later applied to α-picoline,[10] to quinoline,[11–13] and to some of its derivatives.[13]

[2] J. P. Wibaut and J. Overhoff, *Rec. trav. chim.* **47**, 761 (1928).
[3] C. Garner, Brit. Pat., 829,838; *Chem. Abstr.* **54**, 15406 (1960).
[4] K. Lehmstedt and H. Hundertmark, *Ber. deut. chem. Ges.* **62**, 1065 (1929).
[5] A. Albert and J. B. Willis, *J. Soc. Chem. Ind. (London)* **65**, 26 (1946).
[6] W. H. F. Sasse, unpublished work (1960).
[7] G. M. Badger, N. Kowanko, and W. H. F. Sasse, *J. Chem. Soc.* p. 440 (1959).
[8] J. P. Wibaut and L. M. F. van de Lande, *Rec. trav. chim.* **48**, 1005 (1929).
[9] J. P. Wibaut and H. D. T. Willink, *Rec. trav. chim.* **50**, 287 (1931).
[10] H. D. T. Willink and J. P. Wibaut, *Rec. trav. chim.* **54**, 275 (1935).
[11] J. P. Wibaut, H. D. T. Willink, and W. E. Nieuwenhuis, *Rec. trav. chim.* **54**, 804 (1935).
[12] J. G. Breckenridge, R. W. J. Lewis, and L. A. Quick, *Can. J. Research* **17B**, 258 (1939).
[13] J. G. Breckenridge, *Can. J. Research* **28B**, 593 (1950).

In 1960 Rapoport and his co-workers[14] found that some 2,2′-biquinoline is formed when quinoline was used as a solvent for dehydrogenations in the presence of palladium-on-carbon catalyst, and they showed that several related bases (including pyridine) gave 2,2′-biaryls when refluxed at atmospheric pressure with a 5% palladium-on-carbon catalyst. With a pyridine-to-catalyst ratio of 10:1, 11% conversion of pyridine to 2,2′-bipyridine was observed after heating for 24 hr.

Rapoport's findings have been confirmed in the authors' laboratory where the actions of carbon-supported catalysts (5% metal) derived from ruthenium, rhodium, palladium, osmium, iridium, and platinum, on pyridine, have been examined.[15] At atmospheric pressure, at the boiling point of pyridine, and at a pyridine-to-catalyst ratio of 8:1, only palladium was active in bringing about the formation of 2,2′-bipyridine. It was also found that different preparations of palladium-on-carbon varied widely in efficiency (yield 0.05–0.39 gm of 2,2′-bipyridine per gram of catalyst), but the factors responsible for this variation are not known. Palladium-on-alumina[16] was found to be inferior to the carbon-supported preparations and gave only traces of bipyridine.

2. *Raney Catalysts*

In 1956 it was noticed that traces of 2,2′-bipyridine were formed during the hydrogenolysis of certain organosulfur compounds with W-7 Raney nickel,[17] in pyridine as solvent.[18–20] This finding prompted the examination of the actions of several different Raney nickel catalysts on pyridine, and it was found that the amount of 2,2′-bipyridine formed by reaction of W-7 Raney nickel with boiling pyridine (using a pyridine-to-catalyst ratio of 4:1) could be increased from 0.058 to 0.33 gm per gram of catalyst by heating the Raney nickel to 100°C before treatment with pyridine.[1] Although this preliminary treatment could be carried out at atmospheric pressure

[14] H. Rapoport, R. Iwamoto, and J. R. Tretter, *J. Org. Chem.* **25**, 372 (1960).
[15] C. P. Whittle, Ph.D. Thesis, Adelaide, 1962; W. H. F. Sasse and C. P. Whittle, *Australian J. Chem.* In press.
[16] A. C. Johnston, U. S. Patent 2,366,409; *Chem. Abstr.* **39**, 2001 (1945).
[17] H. R. Billica and H. Adkins, *Org. Syntheses* **29**, 24 (1949).
[18] W. H. F. Sasse, Ph.D. Thesis, Adelaide, 1956.
[19] G. M. Badger, N. J. Christie, J. M. Pryke, and W. H. F. Sasse, *J. Chem. Soc.* p. 4417 (1957).
[20] G. M. Badger, *Australian J. Sci.* **21**, P45 (1958).

in the presence of water, it was found advantageous to heat the catalyst *in vacuo* since an almost anhydrous catalyst could be obtained in this way. Such catalysts reacted smoothly with bases less water-soluble than pyridine.[18]

Most of the work with Raney nickel catalysts in these laboratories has been carried out with catalysts which have been heated (degassed) *in vacuo;* but for work on a large scale, it is often convenient to degas the catalyst by heating it at atmospheric pressure in the presence of water or pyridine. A more efficient catalyst, which yields about 0.5 gm of 2,2′-bipyridine per gram of catalyst (after 50 hrs) has been developed,[21] and it has recently been shown that this yield can be raised to about 0.58 gm per gram of catalyst by degassing at 200°C rather than at 100°C. However, catalysts degassed at still higher temperatures have been found to give less 2,2′-bipyridine.[15]

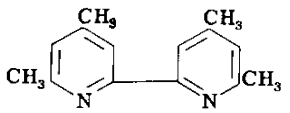
Other factors which are known to lower the yield of 2,2′-bipyridine include dilution of the pyridine with a solvent (such as xylene) and the presence of pyrroles.[21] The formation of pyrroles in the reaction, and the accumulation of 2,2′-bipyridine, are no doubt responsible for the fact that the production of 2,2′-bipyridine ceases after about 50 hr. The catalyst can be used for longer periods only if the reaction is carried out under conditions of continuous flow, or if the products of the reaction are removed as they are formed.

In addition to the Raney nickel catalysts, Raney catalysts derived from iron, cobalt, and copper have been examined for their action on pyridine.[15] At the boiling point of pyridine, degassed Raney iron gave only a very small yield of 2,2′-bipyridine; but the activity of iron in this reaction is doubtful as the catalyst was subsequently found to contain 1.44% of nickel. Traces of 2,2′-bipyridine (detected spectroscopically) were formed from pyridine and a degassed, Raney cobalt catalyst; but several Raney copper catalysts failed to produce detectable quantities of 2,2′-bipyridine following heating with pyridine.

B. The Reaction with Substituted Pyridines

Reaction of α-picoline with a nickel-alumina catalyst has been reported to give a mixture of four isomeric dimethylbipyridines, one of which has been identified at 6,6′-dimethyl-2,2′-bipyridine.[10] With palladium-on-carbon, 2,4-lutidine was found to be more reactive than pyridine,[14] and the isolated biaryl has been assigned the structure (2). However, some confusion arises from the statement that this

[21] W. H. F. Sasse, *J. Chem. Soc.* p. 3046 (1959).



(2)

TABLE I

The Preparation of Substituted 2,2′-Bipyridines from Substituted Pyridines and Degassed Raney Nickel[1,15,22]

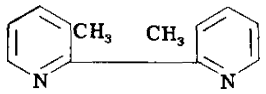
Starting material	2,2′-Bipyridine formed	Yield (gm)[a]
Pyridine	2,2′-Bipyridine	30
α-Picoline	6,6′-Dimethyl-	1.3
2,4-Lutidine	4,4′,6,6′-Tetramethyl-	0.83
2,5-Lutidine	3,3′,5,5′-Tetramethyl-	1.8
	and 5,5′-dimethyl-	1.7
2,4,6-Trimethylpyridine	Several unidentified 2,2′-bipyridines	—
2-Phenylpyridine	6,6′-Diphenyl-	0.14[b]
β-Picoline	5,5′-Dimethyl-	34–53
3-Ethylpyridine	5,5′-Diethyl-	52
3,5-Lutidine	3,3′,5,5′-Tetramethyl-	0.52
	3,3′,5,5′-Tetramethyl-	0.50[c]
3-Benzylpyridine	5,5′-Dibenzyl-	8.75[b]
3-Benzoylpyridine	5,5′-Dibenzoyl-	0.14[b]
Ethyl nicotinate	5,5′-Dicarbethoxy-	5.1[b]
	5,5′-Dicarbethoxy-	11.0[c]
Sodium nicotinate	5,5′-Dicarboxy-	1.0[d]
3,4-Lutidine	4,4′,5,5′-Tetramethyl-	85[c]
3-Ethyl-4-methylpyridine	4,4′-Dimethyl-5,5′-diethyl-	25
	4,4′-Dimethyl-5,5′-diethyl-	53[c]
γ-Picoline	4,4′-Dimethyl-	52–56
4-Ethylpyridine	4,4′-Diethyl-	36–48
4-*n*-Amylpyridine	4,4′-Di-*n*-amyl-	48[c]
4-Benzylpyridine	4,4′-Dibenzyl-	13.0[c]
4-Phenylpyridine	4,4′-Diphenyl-	3.11[b]
4-Benzoylpyridine	4,4′-Dibenzoyl-	0.05[b]
Ethyl isonicotinate	None	—
2-Aminopyridine	None	—
3-Aminopyridine	None	—
3,5-Dibromopyridine	None	—

[a] Yields obtained from catalyst prepared from 125 gm of aluminum-nickel alloy.
[b] In xylene as solvent.
[c] Reaction carried out under reduced pressure at about 140–150°C.
[d] In water as solvent.

[22] W. H. F. Sasse and C. P. Whittle, *J. Chem. Soc.* p. 1347 (1961).

base does not form a colored chelate compound with cuprous ions since a tetramethyl-2,2′-bipyridine having the same melting point, and previously prepared by Linell[23] by reacting 2,4-lutidine with sodium, was reported to form an orange chelate with cuprous ions. The biaryl obtained following reaction of 2,4-lutidine over Raney nickel was found to behave in these respects like the base described by Linell.

Several substituted pyridines have been examined using the degassed Raney nickel, and the results are summarized in Table I. As all the biaryls obtained formed colored chelates with either ferrous or cuprous ions, they must be derivatives of 2,2′-bipyridine. Structural ambiguities cannot arise with 2,2′-bipyridines derived from 2- and 4-substituted pyridines; but 3-substituted pyridines could conceivably give three isomeric 2,2′-bipyridines (e.g., **3**, **4**, **5**). In fact, however, each 3-substituted pyridine so far examined has given only *one* 2,2′-bipyridine.



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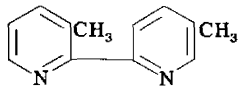

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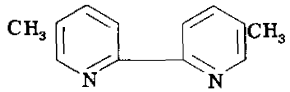


(5)

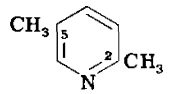
Reaction of β-picoline over degassed Raney nickel was found to give 5,5′-dimethyl-2,2′-bipyridine (**5**), the structure of which was established by its synthesis from 2-bromo-5-methylpyridine.[15] Oxidation of this dimethyl-2,2′-bipyridine, and similar oxidation of the diethyl-2,2′-bipyridine derived from 3-ethylpyridine, gave the corresponding dicarboxylic acid; and the same acid was produced by the action of degassed Raney nickel on sodium nicotinate (in water) or on ethyl nicotinate.[1,15] These transformations established the 5,5′-substitution pattern for three 2,2′-bipyridines derived from 3-substituted pyridines; but such evidence is not available for the biaryls

[23] R. H. Linell, *J. Org. Chem.* **22**, 1691 (1957).

obtained following reaction of degassed Raney nickel with 3-benzylpyridine, 3-benzoylpyridine, 3,4-lutidine, and 3-ethyl-4-methylpyridine. Nevertheless, comparison of the ultraviolet spectra of these bases with the spectra of the corresponding biphenyls supports the view that in these bipyridines the 5,5′-positions are substituted rather than the 3,3′- or 3,5′-positions.[15,22]

Inspection of Table I shows that the yields of 2,2′-bipyridines obtainable from a substituted pyridine in the reaction with degassed Raney nickel depend on the nature of the substituents and their positions in the ring.

Four 2-substituted pyridines were found to give the expected 6,6′-disubstituted 2,2′-bipyridines in yields corresponding to only about 3% of the amount of 2,2′-bipyridine formed from pyridine itself under comparable conditions. It is also of interest that with three 2-methylpyridines the expected 6,6′-dimethyl-2,2′-bipyridines were accompanied by smaller amounts of 2,2′-bipyridines having *no* methyl groups in the 6,6′-positions. Moreover, a very small amount of 5,5′-dimethyl-2,2′-bipyridine (**8**) was isolated following reaction with 2,5-lutidine (**6**) but no 3,3′-dimethyl-2,2′-bipyridine could be detected. The absence of this compound suggests that 3,3′,6,6′-tetramethyl-2,2′-bipyridine (**9**) is not an intermediate, but that the 2-methyl group is lost before the formation of the 2,2′-bipyridine (**6**→**8**).



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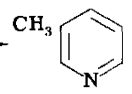

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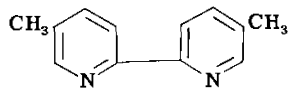

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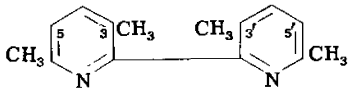


(9)

This view is supported by the observation that small quantities of pyridines which have lost the 2-methyl group are present in the reaction mixture.[22] It may also be noted that γ-collidine gave traces of a mixture of several 2,2′-bipyridines, which reacted with ferrous ions

to form colored chelates, but no pure biaryl could be isolated. Nevertheless, a small quantity of 2,4-lutidine was identified among the products, indicating that some demethylation certainly occurs. No evidence for the loss of the 2-phenyl group in 2-phenylpyridine could be found.

In the absence of an added solvent, 3-alkylpyridines, 4-alkylpyridines, and 3,4-dialkylpyridines all gave yields of substituted 2,2′-bipyridines that were up to three times greater than that of 2,2′-bipyridine from pyridine under similar conditions. With 3-ethyl-4-methylpyridine a marked improvement in yield was observed when the reaction was carried out at about 150°C in a vacuum, rather than at the atmospheric boiling point (195°C) of this base. This effect has also been observed with some other bases; but the amount of 3,3′,5,5′-tetramethyl-2,2′-bipyridine from 3,5-lutidine could not be increased in this way, and this pyridine was as unreactive as the 2-substituted pyridines. This finding is undoubtedly related to the reluctance of 3-substituted pyridines to form 3,3′-disubstituted 2,2′-bipyridines.

Relatively few pyridines with substituents other than alkyl groups have so far been examined, and with some of these the reaction has been carried out only in the presence of added solvent. A comparison of the reactivities of these pyridines is therefore difficult. It has, however, been established that the presence of benzoyl groups in the 3- and 4-positions causes a very marked drop in the yields of the corresponding 2,2′-bipyridines. The 3- and 4-benzylpyridines were found to be more reactive; but even in the absence of solvent, and *in vacuo*, 4-benzylpyridine gave only about one-third of the yield of the 2,2′-bipyridine compared with pyridine itself. Ethyl nicotinate in the absence of solvent and under vacuum[1,22] gave a similar yield of biaryl; but 4-phenylpyridine was found to be less reactive.

Pyridines which failed to produce detectable quantities of 2,2′-bipyridines include 2-aminopyridine, 3-aminopyridine, 3,5-dibromopyridine, and ethyl isonicotinate. 2,2′-Bipyridine failed to give any 2,2′:6′,2′:6″,2‴-quaterpyridine, and this is discussed in a later section.

C. The Reaction with Related Ring Systems

1. *Quinolines*

The three catalysts which have been used for the preparation of 2,2′-bipyridines from pyridines have also been employed for the preparation of 2,2′-biquinolines from quinolines. The results have been summarized in Table II in terms of the percentage conversion of the quinoline into the 2,2′-biquinoline and as yields of the biquinoline obtainable from 100 gm of the quinoline.

TABLE II

The Preparation of 2,2′-Biquinolines with Nickel and Palladium Catalysts: Percentage Conversions[a] and Yields[b]

Starting material	Nickel-alumina[c]	Palladium-on-carbon[d,e]	Degassed Raney nickel[d,f]
Quinoline	3.85 gm (15%)[11–13]	(17%)[14]	5.6 gm (20%)[g,24]
	(10–20%)[13]	2.56 gm (67%)[g,25]	1.8 gm (3.5%)[24]
	—	7.0 gm (70%)[g,25]	—
Quinaldine	—	0[i,14]	0.27 gm (1%)[24]
3-Methylquinoline	—	0[14]	1.2 gm (3%)[24]
Lepidine	(30%)[13]	—	18.5 gm (47%)[j,24]
	—	—	6.1 gm (40%)[24]
2,4-Dimethylquinoline	—	—	0.55 gm (2%)[24]
4-Phenylquinoline	—	(11%)[14] at 360°C	—
6-Methylquinoline	(Up to 1%)[13]	—	2.0 gm (17%)[g,11]
6-Methoxyquinoline	—	(21%)[14] at 265°C	—
7-Methylquinoline	None[13]	—	2.3 gm (7%)[24]
8-Methylquinoline	None[13]	(12%)[14]	—

[a] Calculated on the basis of recovered quinoline; to avoid confusion with yields' percentage conversions are given in parentheses.

[b] Weight of 2,2′-biaryl obtained from 100 gm starting material.

[c] Reactions carried out at ca. 325°C with 12.5 gm of catalyst per 100 gm of base.

[d] Most reactions were carried out at atmospheric boiling points of the bases; exceptions are noted.

[e] With 10 gm of 5% palladium-on-carbon per 100 gm of base; 24 hr.

[f] The ratio catalyst to base was varied from ca. 45 to ca. 60 gm per 100 gm of base; time of reaction varied between 14 and 50 hr; for details see the reference in footnote 24.

[g] Different results were obtained with different preparations of catalyst.

[h] Temperature of the reaction about 110°C (bp at ca. 18 mm).

[i] Formation of 1,2-di(2-quinolyl)ethane reported.

[j] Reaction temperature ca. 140°C (bp at 22 mm).

[k] Refluxed at 20 mm for 14 hr only.

Table II shows that, at least for the reactions with quinoline and with 4-methylquinoline (lepidine), nickel-alumina and degassed Raney nickel catalysts are of similar efficiency; but better yields have been obtained with degassed Raney nickel, and only this catalyst produces the biaryl from 7-methylquinoline.

[24] W. H. F. Sasse, *J. Chem. Soc.* p. 526 (1960).

With quinoline and palladium-on-carbon the yields and conversions with different batches of catalyst were found to vary very widely; but this matter has not been studied in detail, and similar data are still lacking for other quinolines.

Most of the reactions with quinolines and degassed Raney nickels have been carried out at the atmospheric boiling point (above 230°C), a condition which is known to favor the formation of by-products.[24] With quinoline and 4-methylquinoline (lepidine), however, the yields of the 2,2′-biquinolines were increased three to four times by heating *in vacuo* at 150°C, and it seems probable that other quinolines will behave similarly. Table II also shows that the yields of 2,2′-biquinolines obtained under comparable conditions vary with the position of the methyl group in a fashion reminiscent of the trends observed with the pyridines (Table I). This similarity extends to the behavior of the two 2-methyl substituted quinolines studied, which undergo loss of the 2-methyl group to some extent and form traces of 2,2′-biquinolines.

Sufficient data are not yet available to allow evaluation of the relative merits of palladium-on-carbon and degassed Raney nickel catalysts. Comparable yields of 2,2′-biquinolines have been obtained by both methods under suitable conditions; but the percentage conversions with degassed Raney nickel have been found to be much lower, reflecting the extent of side reactions with this catalyst. However, work in this laboratory has shown that the reaction of quinoline with palladium-on-carbon is not free from complications; for example, at least three products in addition to 2,2′-biquinoline have been detected by paper chromatography.

Rhodium-on-carbon has also been found to bring about the formation of 2,2′-biquinoline from quinoline, the yield and the percentage conversion being similar to that obtained with palladium-on-carbon.[25] On the other hand, rhodium-on-carbon failed to produce 2,2′-bipyridine from pyridine,[15] and it has not yet been tried with other bases. Experiments with carbon-supported catalysts prepared from ruthenium, osmium, iridium, and platinum have shown that none of these metals is capable of bringing about the formation of 2,2′-biquinoline from quinoline under the conditions used with palladium and rhodium.[25]

2. *Other Ring Systems*

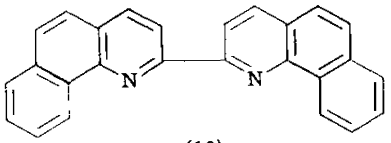
Isoquinoline failed to react when refluxed over palladium-on-carbon,[14] but with degassed Raney nickel it underwent extensive de-

[25] G. D. F. Jackson and W. H. F. Sasse, *Australian J. Chem.* In press.

composition and only trace amounts of 3,3′-biisoquinoline could be isolated.[1]

Benzo[*h*]quinoline was also recovered unchanged after being heated with palladium-on-carbon to 370°C,[14] but (in dilute solution) with degassed Raney nickel it gave a trace of a bibenzo[*h*]quinoline. By analogy with the biaryls obtained from other bases, this is regarded as 2,2′-bibenzo[*h*]quinoline (**10**).[1] It did not form a colored chelate compound with cuprous ions under conditions found to be satisfactory for the formation of a chelate from 2,2′-bibenzo[*f*]quinoline; but this is not surprising in view of the fact that 8,8′-dimethyl-2,2′-biquinoline also fails to form a chelate with cuprous ions.[14]

Under the same experimental conditions benzo[*f*]quinoline gave twenty times as much biaryl (**11**) as the [*h*]-analog; but phenanthridine failed to give a biphenanthridine.[1] Quinoxaline with degassed Raney nickel gave 1,2,3,4-tetrahydroquinoxaline together with 2-methylbenzimidazole. The yield of the biaryl was similar to that of 2,2′-biquinoline from quinoline.[18] Benzothiazole gave 2,2′-bibenzothiazole, but benzimidazole was found to attack the catalyst with the



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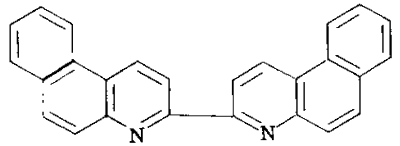


(11)

formation of the nickel salt.[18] Acridine in xylene, and degassed Raney nickel, gave a mixture of 9,10-dihydroacridine and 9,9′,10,10′-tetrahydro-9,9′-biacridine.[1]

D. The Mechanism of the Reaction

1. *The Nature of Raney Nickel*

As most of the work on this reaction has been carried out with degassed Raney nickel, it will be appropriate to summarize briefly current views concerning the nature of this catalyst.

Raney nickel catalysts are prepared by leaching nickel-aluminum alloys with aqueous alkali, and consist mainly of nickel (ca. 77%), aluminum (1–3% as metal, 19.8–21.3% as oxide) and hydrogen.[26-29] The hydrogen content has been shown to vary widely, depending on the age of the catalyst and its mode of preparation; moreover the hydrogen content of a given catalyst can easily be reduced. This has usually been done by heating the catalyst *in vacuo* to a temperature exceeding that of its preparation. It is an exothermic process[21,29] which involves no change in the face-centered-cubic structure,[27] and the temperature at which this process is complete depends on the mode of preparation of the catalyst and its age.[27] With the hydrogen-rich W-6 Raney nickel, it has been found that 85–95% of the hydrogen has been removed when the temperature reaches from 300 to 400°C.[27,28] During this degassing process the surface area of the Raney nickel does not alter appreciably until about 85–95% of the hydrogen has been removed; but at higher temperatures the surface area has been found to decrease rapidly to about 50–75% of its original value.[27,28] These changes are accompanied by a loss of activity of the catalyst in catalytic hydrogenation,[28-30] at least during the initial stages.[28]

The nature of Raney nickel catalysts has been discussed by many authors and widely differing views have been expressed.[28-31] Kokes and Emmett[27,28] have suggested that Raney nickel is promoted by aluminum and that the hydrogen forms a substitutional solution with the nickel. On degassing a catalyst, a nickel-aluminum alloy remains which contains a large number of lattice vacancies, which are available for occupation by hydrogen atoms. Assuming that each hydrogen atom contributes one electron and that each aluminum atom contributes three electrons to the *d*-band of the nickel atoms, they estimate that a W-6 Raney nickel having a 3% aluminum content has about 1.85 added electrons per unit cell, and that this value decreases to about 0.76 when the catalyst is completely degassed. Somewhat lower values have been calculated assuming a 2% aluminum content.[28]

[26] V. N. Ipatieff and H. Pines, *J. Am. Chem. Soc.* **72**, 5320 (1950).
[27] R. J. Kokes and P. H. Emmett, *J. Am. Chem. Soc.* **81**, 5032 (1959).
[28] R. J. Kokes and P. H. Emmett, *J. Am. Chem. Soc.* **82**, 4497 (1960).
[29] H. A. Smith, A. J. Chadwell, and S. S. Kirslis, *J. Phys. Chem.* **59**, 820 (1955).
[30] L. K. Freidlin and N. I. Ziminova, *Chem. Abstr.* **45**, 1836, 6031 (1951).
[31] E. Lieber and F. L. Morritz, *Adv. in Catalysis* **5**, 417 (1953).

2. *The Adsorption of Pyridine on Metal Catalysts*

The outstanding feature of the preparation of 2,2′-bipyridine from pyridine under the influence of metal catalysts is the absence of isomeric bipyridines among the products. In this respect reactions using metal catalysts in a heterogeneous system differ from methods which have been used to prepare bipyridines in homogeneous systems.[32,33]

The exclusive formation of 2,2′-bipyridines from pyridines in the reaction with degassed Raney nickel led to the hypothesis that the reacting species are chemisorbed on the catalyst while the interannular carbon-carbon bond is being formed.[1] Support for this view is found in many observations which demonstrate a tendency on the part of organic bases to be preferentially adsorbed by metal catalysts: effects of this type are commonly noticed during catalytic hydrogenations, the presence of basic compounds causing a retardation of the rates of hydrogenation of unsaturated groups. Examples of the poisoning effects of pyridine include the use of pyridine- and quinoline-poisoned catalysts in the hydrogenation of alkynes to alkenes,[34,35] and the use of quinoline-sulfur poisoned palladium catalysts in the Rosenmund reduction of acid chlorides.[36] The failure of 1,3,5-triazine to undergo hydrogenation over palladium or platinum is an instance of self-poisoning,[37] whereas the concept of preferential adsorption of pyridines by way of their nitrogen atoms has been invoked by Adkins[38] to account for the greater ease of hydrogenation of 2- and 2,6-substituted pyridine. Substituents in these positions evidently interfere with the adsorption via the nitrogen atoms, thus favoring adsorption of the ring via the π-electrons.

Quantitative studies of the effect of pyridine on the rate of hydrogenation of *trans*-crotonic acid in the presence of a platinum catalyst have been carried out by Maxted and Walker[39] who concluded that

[32] G. T. Morgan and F. H. Burstall, *J. Chem. Soc.* p. 20 (1932).
[33] R. H. Linell and A. B. Zahlan, U. S. Patent 2,773,066; *Chem. Abstr.* **51**, 5845 (1957).
[34] L. Ruzicka and P. Müller, *Helv. Chim. Acta* **22**, 755 (1939).
[35] O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta* **30**, 1911 (1947).
[36] E. B. Hershberg and J. Cason, *Org. Syntheses, Collective Vol.* **III**, 627 (1955).
[37] C. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.* **77**, 44 (1955).
[38] H. Adkins, L. F. Kuick, M. Farlow, and B. Wojcik, *J. Am. Chem. Soc.* **56**, 2425 (1934).
[39] E. B. Maxted and A. G. Walker, *J. Chem. Soc.* p. 1093 (1948).

the poisoning effect is dependent upon the availability of the lone-pair electrons of the nitrogen atom for bonding to the catalyst. More recently, the effect of pyridine on the rates of hydrogenation of *trans*-crotonic acid in the presence of several different Raney catalysts has been measured.[40] All the Raney nickel catalysts examined in this way were poisoned by pyridine, and each was found to be effective in promoting the formation of 2,2′-bipyridine from pyridine. On the other hand, a Raney cobalt catalyst which failed to produce any 2,2′-bipyridine, was not detectably affected by pyridine as far as its ability as a hydrogenation catalyst is concerned. These results support the view that the chemisorption of the pyridine to the catalyst is a necessary prerequisite for the formation of 2,2′-bipyridine from pyridine.

During this work it was noticed that the Raney nickel catalysts which were less effective in the preparation of 2,2′-bipyridine were more efficient in the hydrogenation of *trans*-crotonic acid, and their activity in this latter reaction was less affected by pyridine. These trends suggested that the interaction of pyridine with Raney nickel can be hindered by the hydrogen in the lattice of the catalyst. Subsequently, this point was examined by studying the formation of 2,2′-bipyridine with Raney nickel catalysts which had been prepared under identical conditions, but which had been degassed at temperatures varying from 30 to 400°C.[15] The results obtained (Table III) showed that the hydrogen content of the catalyst is, indeed, one of the major factors influencing the activity of the Raney nickel catalyst in the formation of 2,2′-bipyridine. If it is assumed that vacancies created by removal of hydrogen from the lattice are available for occupation by pyridine, then it might be thought that the maximum activity should be observed with catalysts which have been degassed near 400°C. In fact, however, activity begins to fall off for catalysts degassed above 200°C, and it is suggested that annealing of the catalyst begins at this temperature.[15] Kokes and Emmett[27] have shown that the surface area of a commercially available Raney nickel catalyst begins to decrease sharply with increasing temperature for catalysts degassed above 250°C, and with W-6 Raney nickel this temperature was found to be near 350°C.[28] In the absence of data for the surface area of the degassed W-7 Raney nickel used in the reaction with pyridine, this point remains in doubt. However it should be pointed

[40] G. M. Badger, G. D. F. Jackson, and W. H. F. Sasse, *J. Chem. Soc.* p. 4438 (1960).

out that the relationship apparent from Table III is approximately the opposite of that noted by Kokes and Emmett[28] for the activity of degassed W-6 Raney nickel in the parahydrogen conversion and in the hydrogenation of ethylene. As these authors have proposed that the

TABLE III
REACTION BETWEEN PYRIDINE AND W-7 RANEY NICKEL CATALYSTS: YIELDS OF 2,2′-BIPYRIDINE AND OF COMPLEX[15,21]

Temperature (°C) of degassing the catalyst	Length of reaction (hr)	2,2′-Bipyridine[b] (gm)	Complex (gm)	Ratio[c]
30	50	15.75	1.4	8.9
100	50	30.0	1.5	5
200	50	35.25	1.5	4.25
250	50	31.0	0.65	2.1
300	50	26.0	0.35	1.35
400	50	23.5	0.3	1.20
100	11	20	0.5	2.5
100	187	30	4.0	7.5
100	46 (1% Pyrrole added)	26	2.5	9.6
100	53 (10% Pyrrole added)	3	0.8	37.5
100	Flow rate 150 ml. per hour[a]	5	0.04	0.8
100	Flow rate 50 ml. per hour[a]	16	0.8	5

[a] Reaction carried out by passing pyridine over the catalyst in a column; for details see the reference in footnote 21.

[b] Yield obtained from 250 ml. of pyridine and catalyst prepared from 125 gm of 1:1 aluminum-nickel alloy.

[c] 100 × Weight of complex/weight of 2,2′-bipyridine.

activity of W-6 Raney nickel in these reactions is related to the number of added electrons per unit cell of the catalyst, the relationship illustrated by Table III may imply that the formation of 2,2′-bipyridine from pyridine has the opposite electronic requirements as far as the number of added electrons per unit cell in Raney nickel is concerned.

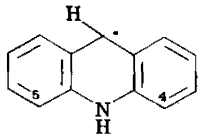
3. *The Formation of the Interannular Carbon-Carbon Bond*

The discussion in the previous section suggests that adsorption of pyridine on the catalyst is a necessary prerequisite for the formation of 2,2′-bipyridine; but as platinum catalysts, which are poisoned by

pyridine, do not bring about the formation of 2,2′-bipyridine,[15,18] adsorption is not a sufficient condition for the occurrence of the reaction.

In order to account for the activation of the chemisorbed pyridine by Raney nickel, it has been suggested that one atom of hydrogen is transferred from the catalyst to the adsorbed pyridine and that the resulting complex has a hybrid structure in which the 2-, 4-, and 6-positions have some radical character.[1,18,20] If two of these species are suitably situated on the catalyst surface, then combination could occur only in such a way as to give a 1,1′,2,2′-tetrahydro-2,2′-bipyridine. If, however, the nitrogen-nickel bond is rather weak, then some of the radicals would be expected to leave the surface of the catalyst; and if their average lifetime is sufficient, their concentration in the liquid could become large enough to allow combination to occur in the homogenous phase. Combination in the latter manner would be expected to give a mixture of isomeric tetrahydrobiaryls.

As all the pyridines so far examined have given only 2,2′-bipyridines, it seems that the interannular carbon-carbon bonds must be formed while the intermediates are bonded to the catalyst. The only exception is acridine, which has no free α-position and which gave 9,9′,10,10′-tetrahydro-9,9′-biacridine, presumably by combination of two intermediate radicals (12) in the solution. It seems probable that



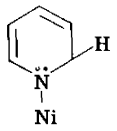
(12)

interaction of the 4- and 5-hydrogen atoms in the adsorbed acridine would considerably weaken the nickel-nitrogen bond, and the electronic effect of the extended conjugated system would weaken this bond further and so stabilize the radical (12) that combination in solution occurs.

Except for the tetrahydrobiaryls derived from acridine and from quinoxaline, the postulated intermediate tetrahydrobipyridines have not been isolated; but such compounds may be too unstable under the conditions of the reaction to permit their isolation. Evidence is, therefore, still lacking for the last two steps of dehydrogenation and desorption from the catalyst. Dehydrogenation could conceivably occur while the tetrahydro derivative is still adsorbed on the catalyst,

thus making the excess hydrogen atoms available for the activation of further adsorbed molecules of pyridine. Alternatively, desorption could precede dehydrogenation of the tetrahydrobipyridine. If this occurred with complete loss of the liberated hydrogen from the system, then the catalyst would have to supply 1 gm mole of hydrogen per gram mole of 2,2′-bipyridine formed. This condition could not be fulfilled with Raney nickel catalysts which have been degassed at temperatures above about 150°C. For example, the catalyst degassed at 400°C gave 2,2′-bipyridine corresponding to 50 ml. hydrogen per gram of catalyst, a value which is far in excess of the hydrogen content of similar catalysts examined by Kokes and Emmett.[27,28] Considerations of this type prompted the suggestion[15] that hydrogen from the catalyst is not involved in the formation of 2,2′-bipyridine from pyridine, but that transfer of an electron through the nickel-nitrogen bond to the electron-deficient adsorbed pyridine occurs. An electron displacement of this type would result in the appearance of an uncoupled electron at either the 2-, 4-, or 6-position, and coupling between suitably placed intermediates (13) would be expected to give (14). The charge transferred would be derived from the added electrons present in the lattice and originating not only from the aluminum and hydrogen but possibly from adsorbed pyridine molecules as well.

It is not obvious how the adsorbed 2,2′-dihydro-2,2′-bipyridine (14) could leave the catalyst without undergoing dehydrogenation either simultaneously or before desorption. This second alternative could however be rationalized if it is assumed that in the preparation of 2,2′-bipyridine the two molecules of pyridine are bonded to *one* atom of nickel (15). The formation of the carbon-carbon bond could



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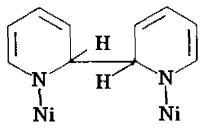

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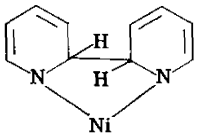


(15)

then be regarded as the formation of a chelate ring, and the energy required for the dehydrogenation could be derived from the formation of this ring. This implies that dehydrogenation occurs while the hydrogenated bipyridine is held on the catalyst. In this connection

it may be added that the dimensions of the lattice of Raney nickel seem to preclude the bonding of one molecule of 2,2′-bipyridine to two adjacent nickel atoms.

4. *Factors Affecting the Ease of Formation of 2,2′-Bipyridines*

It seems therefore that four stages can be distinguished in the reaction leading from pyridine to 2,2′-bipyridine: the adsorption of the starting material, the activation of the adsorbed species to form the interannular carbon-carbon bond, the dehydrogenation of the hydrogenated biaryl, and the desorption. Little evidence can be offered for the last two stages; their order can doubtless be reversed, and in some cases dehydrogenation need not occur at all. In this section we intend to discuss the variations in yields, as summarized in Tables I and II, in terms of these four stages of the reaction.

The low yields of 6,6′-disubstituted-2,2′-bipyridines recorded in Table I are probably the result of steric retardation of the adsorption of 2-substituted pyridines. This view is supported by the observation that 2-methylpyridine is a much weaker poison for catalytic hydrogenations than pyridine.[15] On the other hand, the quinolines so far examined (Table II) are more reactive; but with these compounds the steric effect of the fused benzene ring could be partly compensated by the additional stabilization of the adsorbed species, since the loss of resonance energy accompanying the localization of one π-electron would be smaller in a quinoline than in a pyridine derivative.

It would be expected that the stabilization of the adsorbed species by an extended conjugated system should increase with the number of aromatic rings in the adsorbed azahydrocarbon. However, data suitable for comparison are available only for phenanthridine, benzo[*f*]quinoline, and benzo[*h*]quinoline.[1] The large difference in the yields of biaryl obtained from the last two bases could be caused by steric interaction of the 7,8-benz-ring with the catalyst, which would lower the concentration of the adsorbed species relative to that with benzo[*f*]quinoline. The failure of phenanthridine to yield any biaryl is also noteworthy since some 5,6-dihydrophenanthridine was formed.[1,18] This suggests that adsorption on the catalyst via the nitrogen atom is possible, but that steric inhibition to the combination of the activated species is involved. The same effect could be responsible for the exclusive formation of 5,5′-disubstituted 2,2′-dipyridines from 3-substituted pyridines, as well as for the low yields of 3,3′,5,5′-tetramethyl-2,2′-bipyridines obtained from 3,5-lutidine and of 3,3′-dimethyl-2,2′-biquinoline from 3-methylquinoline. If it is assumed that some freedom of rotation about the nickel-nitrogen bond is permitted and if the 3,3′-substituents in the intermediate are close enough to interact, then the adsorbed species would clearly rearrange preferentially to form the 5,5′-disubstituted-2,2′-bipyridines. Similarly, with 3,5-disubstituted pyridines, combination of the intermediates would be inhibited, leading to very small yields of product. Models indicate that the extent of 3,3′-interaction in the intermediate hydrogenated 2,2′-bipyridine depends on the hybridization of the nitrogen atoms and that it increases as sp^2 hybridization is approached. These considerations favor intermediates of type (**15**) rather than tetrahydro-2,2′-bipyridines, provided the nitrogen atoms are in a planar configuration.

The electronic effects of substituents in the 3- and 4-positions must affect the availability of the lone-pair electrons of the nitrogen atom for bonding to a nickel atom. Electron-donating substituents would be expected to cause an increase in the concentration of the adsorbed species on the catalyst, thereby increasing the number of combinations taking place and vice versa. The activity of a given pyridine in the formation of a bipyridine should therefore be approximately related to its base strength. Tables I and II reflect this trend, but complications arise from functional groups containing either lone-pair electrons or multiple bonds, which may also interact with the catalyst. This lack of specificity at the first stage of the reaction leading from pyridines to 2,2′-bipyridines is the most serious limitation to the general applicability of this method for the preparation of substituted 2,2′-bipyridines from pyridines with Raney nickel catalysts.

III. Side Reactions

Several products other than 2,2′-biaryls have been isolated following reaction of pyridines with metal catalysts. From the reaction of α-picoline with nickel-alumina, Willink and Wibaut[10] isolated three dimethylbipyridines in addition to the 6,6′-dimethyl-2,2′-bipyridine; but their structures have not been elucidated. From the reaction of quinaldine with palladium-on-carbon, Rapoport and his co-workers[14] obtained a by-product which they regarded as 1,2-di(2-quinolyl)-ethane. From the reactions of pyridines and quinolines with degassed Raney nickel several different types of by-product have been identified. The structures and modes of formation of these compounds are of interest as they lead to a better insight into the processes occurring when pyridines interact with metal catalysts.

A. By-products from the Reaction of Pyridines with Degassed Raney Nickel

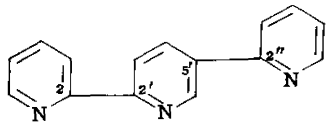
1. *Polypyridines*

The crude 2,2′-bipyridine obtained from the reaction of pyridine and degassed Raney nickel was found to contain 1.5% of 2,2′:6′,2″-terpyridine,[1] but no 2,2′:2′,2″:6″,2‴-quaterpyridine could be detected. Moreover, experiments with 2,2′-bipyridine and Raney nickel have failed to yield quaterpyridine, and the amount of terpyridine formed in experiments with mixtures of pyridine and 2,2′-bipyridine was found to be no higher than in the reaction with pyridine itself.[15]

If it is assumed that 2,2′-bipyridine is bonded to the catalyst by both nitrogen atoms, then the position of the chemisorbed molecule on the metal is rigidly fixed. Unless two molecules of this base can be adsorbed at the required distance from each other and in an arrangement which is close to linear, overlap of the uncoupled electrons at the α-position cannot occur. The failure to detect any quaterpyridine would then indicate that nickel atoms of the required orientation are rarely, if ever, available. Clearly the probability of carbon-carbon bond formation is greater between one chemisorbed molecule of 2,2′-bipyridine and one of pyridine, as the latter can correct its orientation relative to the fixed 2,2′-bipyridine by rotation around the nitrogen-nickel bond, at least within certain limits.

This argument rests on the hypothesis that 2,2′-bipyridine is linked to the catalyst via both nitrogen atoms. This view is supported by the observation that related pyridines and 2,2′-bipyridines have about the same activity as poisons for the hydrogenation of *trans*-crotonic acid.[15] Under the conditions of high dilution used for these experiments, it seems that the pyridine or substituted pyridine molecules are bonded to the nickel atoms so that one molecule of base is bonded to one atom of nickel. If the corresponding 2,2′-bipyridine is linked to the catalyst by bonding both nitrogen atoms to one nickel atom, then a similar activity as a poison would be expected. On the other hand, if adsorption of the 2,2′-bipyridine occurred through only one nitrogen atom, such compounds would be expected to be *less* active as poisons, just as other α-substituted pyridines are less active in this respect than pyridines having no α-substituent.

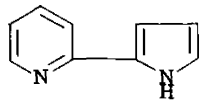
From the dimensions of the lattice of W-6 Raney nickel, it seems that the formation of 2,2′:6′,2″-terpyridine would be expected when one molecule of 2,2′-bipyridine and one molecule of pyridine are adsorbed on adjacent nickel atoms, separated by about 2.5 Å. Moreover, models suggest that adsorption of one molecule of 2,2′-bipyridine and one molecule of pyridine on two nickel atoms which are separated by about 5 Å should lead to the formation of 2,2′:5′,2″-terpyridine (**16**). This base has been found in the crude 2,2′-bipyridine to the extent of about 0.1%.[15]



(16)

2. *The Formation of Pyrroles from Pyridines*

The most important by-product formed in the reaction of pyridine with degassed Raney nickel is an organonickel complex[1] which has been shown to be a complex of one molecule of 2,2′-bipyridine, two molecules of 2,2′-pyrrolylpyridine (**17**), and one nickel II ion.[41] It is significant that, although the formation of 2,2′-bipyridine ceases after 50 hr refluxing, the formation of this complex continues for at least another 140 hr.



(17)

Some of the factors which affect the relative yields of 2,2′-bipyridine and of the organonickel complex are known.[21] For example, the addition of about 1% pyrrole to the pyridine during the reaction causes a 60% increase in the yield of the complex and a 13% decrease in the amount of 2,2′-bipyridine formed (see Table III). When more pyrrole is present the yields of both products are lowered, but the ratio of complex to 2,2′-bipyridine is increased by a factor of about 7. These findings suggest that pyrrole can be incorporated into the complex, presumably by reaction between pyrrole and pyridine to

[41] A. M. Sargeson and W. H. F. Sasse, *Proc. Chem. Soc.* p. 150 (1958).

give 2,2′-pyrrolylpyridine (**17**), followed by further reaction with the catalyst.

Because the complex is formed even when the pyridine used initially contains less than 0.0001 vol. % of pyrrole, it seemed that some pyrrole must be formed from pyridine under the influence of the catalyst. A search for pyrrole among the reaction products revealed that traces of pyrrole could be detected within minutes of the beginning of the reaction; but even after refluxing over the catalyst for 5 days the recovered pyridine contained only about 1 vol. % of pyrrole.

During this work the presence of small quantities of piperidine and α-picoline were also noticed. The exact mode of formation of these products remains to be elucidated, but the formation of piperidine shows that sufficient hydrogen remains on the catalyst to bring about some hydrogenation of the pyridine.

The literature contains several reports[42,43] of the formation of complex mixtures of five- and six-membered aromatic and reduced nitrogen heterocycles following hydrogenation of pyridines in the presence of metal catalysts at temperatures and pressures exceeding those used in the reactions with degassed Raney nickel. As the yield of the organonickel complex is lower when the Raney nickel catalysts used have been degassed at temperatures exceeding 200°C (Table III), it seems that the formation of traces of pyrrole and α-picoline is a consequence of reactions involving hydrogen on the catalyst and proceeding via hydrogenated intermediates.

B. By-products from the Reaction with Quinolines

A systematic study of the by-products formed with degassed Raney nickel and quinoline, and several methylquinolines, has been reported.[24] The results, which have been summarized in Table IV, show that in addition to the formation of 2,2′-biquinolines, the hetero ring undergoes a series of bond-breaking and bond-forming processes. The formation of aniline and *o*-toluidine, shows that the hetero ring can be degraded, and the presence of indole, 3-methylindole, and carbazole suggests that some intermediates may undergo cyclization. The fate of the carbon atoms which are lost is not known, but the fact that quinaldine is a major by-product is of interest. The isolation from

[42] J. I. Jones, *J. Chem. Soc.* p. 1392 (1950); R. I. Jones and A. S. Lindsey, *ibid.* 3261 (1952).

[43] W. S. Ssadikow and A. W. Michailov, *Ber. deut. chem. Ges.* **61**, 421 (1928).

TABLE IV

By-products in the Reaction of Quinolines with Degassed Raney Nickel[24,a]

Starting material	Indoles[b]	$(CH_2)_2$ (gm)	Carbazole (gm)	Bases
Quinoline	4.4 gm (25%)	0.27	0.027	Quinaldine, aniline, *o*-toluidine, 1,2,3,4-tetrahydroquinoline
Quinaldine	0.18 gm (80%)	0.036	0.009	Quinoline, aniline, *o*-toluidine, *N*-ethylaniline
3-Methylquinoline	0.136 gm (60%)	0.09	0.27	Aniline, *o*-toluidine, two unidentified bases
Lepidine	0.0176 gm (80%)	0.076	0.037	Aniline, five unidentified bases
7-Methylquinoline	1.77 gm (15%)[c]	0.01	None	Not examined
2,4-Dimethylquinoline	0.127 gm (65%)	0.013	0.027	Quinoline, 4-methylquinoline, several unidentified bases.

[a] All yields are calculated for 100 gm starting material. Conditions are described in the reference in footnote 24.

[b] Yield of mixture of indole and 3-methylindole; the percentage of 3-methylindole is given in parentheses.

[c] Mixture of 6-methylindole and 3,6-dimethylindole with the percentage of the latter in parentheses.

all these reactions of an alkane, having the properties of a low molecular weight polymethylene, may also be important.

It seems likely that these products arise from processes which are initiated by the hydrogen of the catalyst. Several examples of the fission of the hetero ring of quinoline under the influence of hydrogen and nickel catalysts have been reported. Padoa and Carughi[44] have described the formation of *o*-toluidine and of 2-methylindole from quinoline, hydrogen, and reduced nickel at 260–280°C, but it is believed that this identification was in error and that the compound was actually 3-methylindole. Padoa and Scagliarini[45] obtained aniline and 3-methylindole from 1,2,3,4-tetrahydroquinoline under similar conditions. Padoa proposed that the first step in these reactions is the formation of *o*-alkylanilines, and that this is followed by cyclodehydrogenation to give indoles. Examples of the formation of indoles from *o*-alkylanilines and from *N*-alkyl-*o*-alkylanilines are well known,[46] but the absence of alkylindoles other than 3-methylindole among the by-products from the reactions of degassed Raney nickel and quinoline, quinaldine, 3-methylquinoline, lepidine, and 2,4-dimethylquinoline cannot be accommodated in this scheme.

Work in progress in this department[25] has shown that small quantities of indoles are formed from *o*-alkylanilines and degassed Raney nickel; but the stepwise degradation of the alkyl side chain appears to be a more important process. This may provide an explanation for the formation of aniline and of *o*-toluidine from quinoline. During this work it was found that aniline is not stable to the catalyst, but reacts slowly to give *inter alia* small quantities of 2,2′-diaminobiphenyl, diphenylamine, and carbazole. These findings provide a pathway from *o*-alkylanilines to carbazole; but the initial breakdown of the hetero ring of quinoline remains to be studied. Work with 1,2,3,4-tetrahydroquinoline has shown that this base gives rise to all the products isolated following reaction of degassed Raney nickel with quinoline, and it therefore seems very probable that the hydrogenation of quinoline to 1,2,3,4-tetrahydroquinoline is the first step in the sequence of changes leading to all the products other than 2,2-biquinoline.

[44] M. Padoa and A. Carughi, *Atti reale accad. Lincei, Rend.* (I) **15**, 113 (1906).
[45] M. Padoa and G. Scagliarini, *Atti reale accad. Lincei, Rend.* **17**, 730 (1908).
[46] M. Padoa and O. Carrasco, *Atti reale accad. Lincei, Rend.* (I) **15**, 701 (1906); A. Baeyer and H. Caro, *Ber. deut. chem. Ges.* **10**, 692 (1877); T. Lesiak, *Roczniki Chem.* **31**, 1957 (1957); C. Hansch and G. Helmkamp, *J. Am. Chem. Soc.* **73**, 3080 (1951).

Recent Advances in Quinoxaline Chemistry

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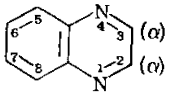
The aim of the present review is to report in broad outline the progress in quinoxaline chemistry since about 1955; previous reviews of the quinoxaline literature are to be found in three major reference

works.[1-3] In recent years there has been much general interest in heterocyclic *N*-oxides and recent work on quinoxaline *N*-oxides has been stimulated both by the interesting rearrangement reactions these compounds undergo[4,5] and also by their biological activity. Thus 2-hydroxymethyl-3-methylquinoxaline 1,4-dioxide, a metabolite of 2,3-dimethylquinoxaline 1,4-dioxide, is highly active against Gram-negative bacteria.[6] Recent work has also led to the preparation of numerous reduced quinoxalines and more unusual derivatives of this type include quinoxaline spirohydantoins, e.g. (**11**), and quinoxaline spiroindoles, e.g. (**104**).

The numbering of the quinoxaline ring system is as shown, the 2 and 3 positions are designated alternatively α positions.



I. Synthesis

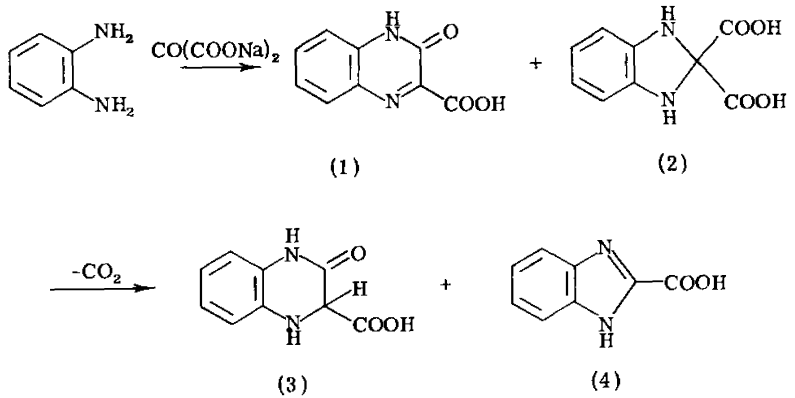
A. Preparation of Quinoxalines from *o*-Diamines

The classical synthesis of quinoxalines involves the condensation of an aromatic *o*-diamine and an α-dicarbonyl compound.

This reaction is so facile that it is of value both for preparative and characterization purposes. Benzil and phenanthraquinone are convenient reagents for the characterization of *o*-diamines, and *o*-phenylenediamine is used commonly for the characterization of α-dicarbonyl compounds.

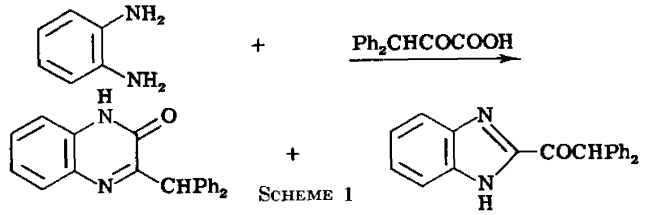
[1] J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings." Interscience, New York, 1953.
[2] Y. T. Pratt, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, Chapter 10. Wiley, New York, 1956.
[3] G. R. Ramage and J. K. Landquist, *in* "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. IV B, Chapter XV. Elsevier, Amsterdam, 1959.
[4] J. W. Clark-Lewis and G. F. Katekar, *J. Chem. Soc.* p. 2825 (1959).
[5] M. S. Habib and C. W. Rees, *J. Chem. Soc.* p. 3371 (1960).
[6] J. Francis, J. K. Landquist, A. A. Levi, J. A. Silk, and J. M. Thorp, *Biochem. J.* **63**, 455 (1956).

The condensation of α-ketoacids and *o*-phenylenediamines gives quinoxalin-2-ones,[7] and mesoxalic acid and *o*-phenylenediamine undergo the expected condensation reaction to give quinoxalin-3-one-2-carboxylic acid (**1**). With sodium mesoxalate an anomalous reaction occurs, the initial products (**1**) and 1,2-dihydrobenzimidazole-2,2-dicarboxylic acid (**2**) undergo an intermolecular hydrogen transfer reaction to yield 1,2,3,4-tetrahydro-3-oxoquinoxaline-2-carboxylic acid (**3**) and benzimidazole-2-carboxylic acid (**4**).[8]



This transfer of hydrogen occurs even when a vigorous stream of oxygen is passed through the reaction mixture. 1,2-Dihydrobenzimidazole-2,2-dicarboxylic acid (**2**), rather than its decarboxylation product, 1,2-dihydrobenzimidazole-2-carboxylic acid, is thought to be the reducing agent since the latter compound is not stable in the presence of oxygen.

The condensation of diphenylpyruvic acid and *o*-phenylenediamine

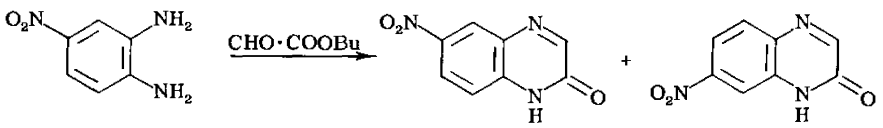


SCHEME 1

[7] D. C. Morrison, *J. Am. Chem. Soc.* **76**, 4483 (1954).
[8] E. C. Taylor and M. J. Thompson, *J. Org. Chem.* **26**, 3511 (1961).

yields a mixture of the quinoxalin-2-one and 2-diphenylacetylbenzimidazole (Scheme 1).[8a]

Reaction of *o*-phenylenediamine and *n*-butyl glyoxylate gives quinoxalin-2-one in excellent yield; with 4-nitro-*o*-phenylenediamine (**5**) a mixture of 6- and 7-nitro-quinoxalin-2-ones, (**6**) and (**7**), is obtained.[9]



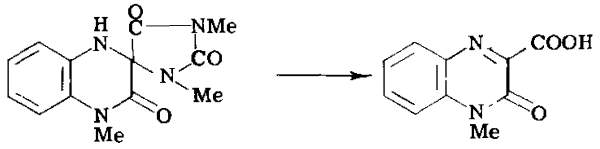
(5) (6) (7)

The corresponding reaction with 2-methylamino-5-nitroaniline affords an unambiguous synthesis of 1-methyl-6-nitroquinoxalin-2-one, the *N*-methyl derivative of (**6**); this product is also obtained by treatment of (**6**) with methyl iodide and methanolic sodium methoxide.[10]

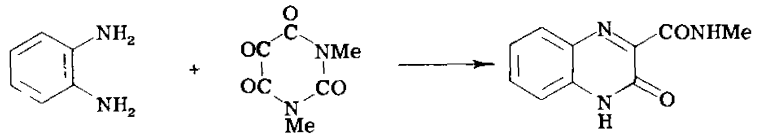
Condensation of *o*-phenylenediamine or *N*-methyl-*o*-phenylenediamine with alloxan (**8**) in neutral solution gives the ureides (**9**) and (**10**), respectively.[11] However, reaction of *o*-phenylenediamine with 1,3-dimethylalloxan (**13**) yields quinoxalin-3-one-2-carboxymethylamide (**14**), rather than the dimethyl ureide.[12,13] Methylation of (**9**) in acetone in the presence of potassium carbonate gives the spirohydantoin (**11**).

(8) (9) : R = H
(10) : R = Me

[8a] M. Pailer, G. Pruckmayr, H. Zellner, and G. Zellner, *Monatsh. Chem.* **93**, 1005 (1962).
[9] C. M. Atkinson, C. W. Brown, and J. C. E. Simpson, *J. Chem. Soc.* p. 26 (1956).
[10] G. W. H. Cheeseman, *J. Chem. Soc.* p. 1246 (1961).
[11] F. E. King and J. W. Clark-Lewis, *J. Chem. Soc.* p. 3379 (1951).
[12] H. Bredereck and W. Pfleiderer, *Chem. Ber.* **87**, 1119 (1954).
[13] W. Pfleiderer, *Chem. Ber.* **88**, 1625 (1955).

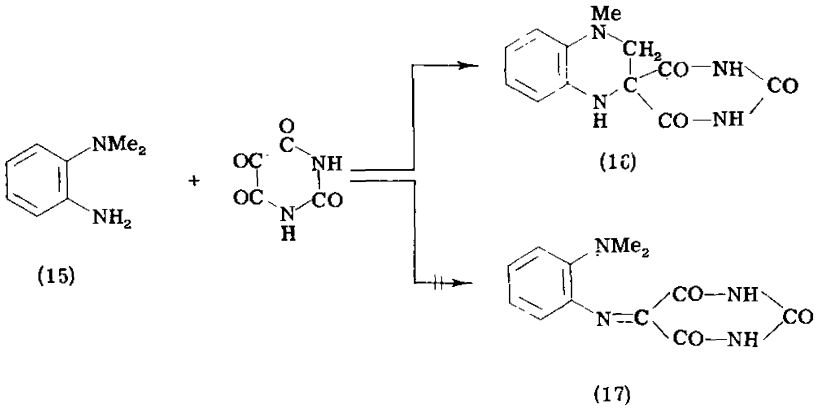


(11) (12)



(13) (14)

The structure of this compound is confirmed by the preparation of the 1-acetyl derivative, acid degradation to 4-methylquinoxalin-3-one-2-carboxylic acid (**12**), and alternative synthesis from the acid chloride of (**12**) and *NN'*-dimethylurea.[14] A most unusual cyclization occurs when *NN*-dimethyl-*o*-phenylenediamine (**15**) is treated with alloxan in ethanolic solution: this apparently involves an *N*-methyl group and leads to the formation of the spirobarbituric acid (**16**). The struc-



(15) (16)

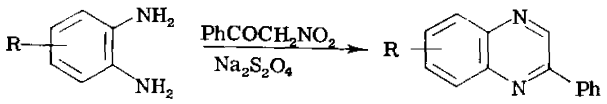
(17)

[14] J. W. Clark-Lewis, *J. Chem. Soc.* p. 422 (1957).

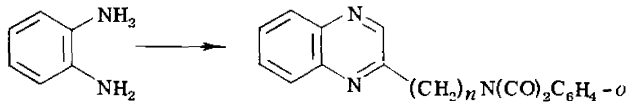
ture of (16) has not so far been confirmed by synthesis; it was formulated originally as the anil (17).[15,16]

The condensation reactions of aromatic *o*-diamines and sugars and sugar derivatives have been studied in detail and quinoxaline derivatives have been prepared recently from osones, osonehydrazones, and dehydro-L-ascorbic acid.[17]

The reaction of *o*-diamines with ω-nitroacetophenone in the presence of sodium dithionite furnishes 2-phenylquinoxalines, and reaction of *o*-phenylenediamine with *p*-$NO_2C_6H_4COCH_2NO_2$ similarly gives 2-(4′-nitrophenyl)quinoxaline:[18]



A versatile synthesis of 2-aminoalkylquinoxalines involves the intermediate preparation of phthalimido derivatives of the type: *o*-$C_6H_4(CO)_2N(CH_2)_nCOCH{=}NC_6H_4NMe_2$-*p*. Condensation of these derivatives with *o*-phenylenediamine yields 2-phthalimidoalkylquinoxalines (18).



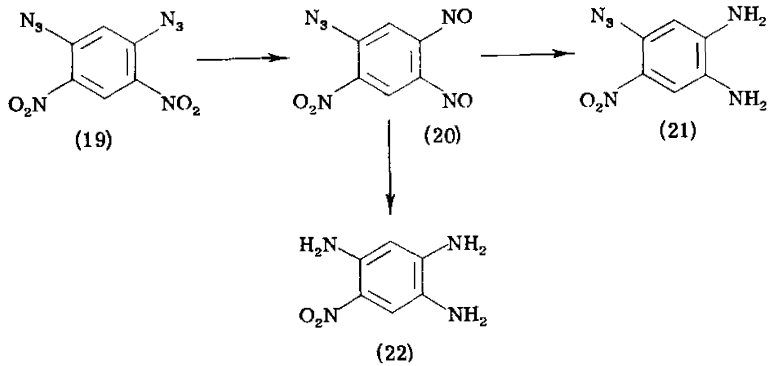
(18)

3-Cyano derivatives of (18) are prepared by reaction of *o*-phenylenediamine with *o*-$C_6H_4(CO)_2N(CH_2)_nCOC(CN){=}NC_6H_4NMe_2$-*p*. Hydrolysis of the latter compounds give intermediates of the type *o*-$C_6H_4(CO)_2N(CH_2)_nCOCOCN$ which on condensation with *o*-phenylenediamine yield 3-phthalimidoalkylquinoxalin-2-ones.[19]

6,7-Disubstituted quinoxalines have been prepared from 2,4-diazido-1,5-dinitrobenzene (19), which on pyrolysis is converted into 2-azido-

[15] F. E. King and J. W. Clark-Lewis, *J. Chem. Soc.* p. 3080 (1951).
[16] J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.* p. 2401 (1959).
[17] G. Henseke and co-workers, *Chem. Ber.* **91**, 101 (1958); *ibid.* **92**, 501, 1550 (1959).
[18] A. Dornow and W. Sassenberg, *Ann.* **594**, 185 (1955).
[19] J. Borkovec, J. Michalsky, and their co-workers, *Chem. listy* **48**, 717, 865 (1954); *ibid.* **49**, 1379, 1405 (1955). *Chem. Abstr.* **49**, 9662 (1955); *ibid.* **50**, 5681 (1956).

1-nitro-4,5-dinitrosobenzene (20)[19a] with loss of nitrogen. Partial reduction of (20) with hydriodic acid gives 1,2-diamino-4-azido-5-nitrobenzene (21) and treatment with excess of hydriodic acid gives 2,4,5-triaminonitrobenzene (22). Reaction of (21) and (22) with α-dicarbonyl compounds furnishes the corresponding 6-azido-7-nitro- and 6-amino-7-nitro-quinoxalines.[20] Pyrolysis of 6-azido-7-nitro-2,3-diphenylquinoxaline (23) gives 6,7-dinitroso-2,3-diphenylquinoxaline (24)[19a] which exists in a red and in a blue-black form. Each modification is reduced by hydriodic acid to 6,7-diamino-2,3-diphenylquinoxaline.[21]

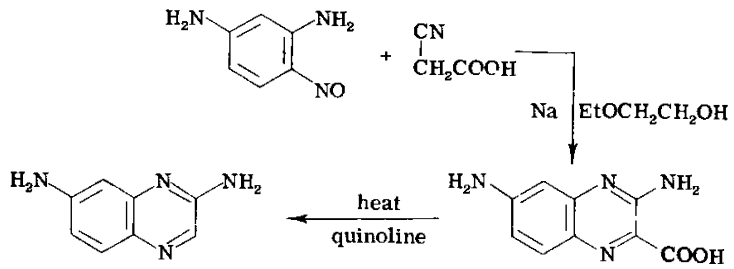


B. Preparation of Quinoxalines from *o*-Nitrosoamines

The condensation of aromatic *o*-nitrosoamines with cyanoacetic acid or cyanoacetamide affords an unambiguous synthesis of un-

[19a] *o*-Nitroso compounds have now been shown to exist as benzoxadiazole *N*-oxides (see A. R. Katritzky, S. Øksne, and R. K. Harris, *Chem. & Ind. (London)* p. 990 (1961).
[20] J. H. Boyer, R. S. Burkis and U. Toggweiler, *J. Am. Chem. Soc.* **82**, 2213 (1960).
[21] J. H. Boyer and R. S. Burkis, *J. Am. Chem. Soc.* **82**, 2216 (1960).

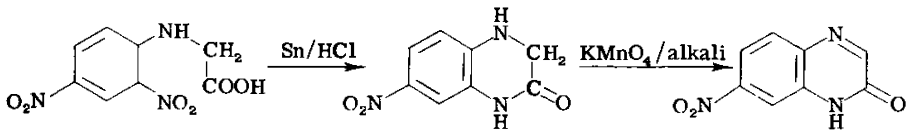
symmetrically substituted quinoxalines and is illustrated by the preparation of 3,6-diaminoquinoxaline (Scheme 2).[22]



SCHEME 2

C. PREPARATION OF QUINOXALINES USING α-AMINO ACID INTERMEDIATES

This method is widely applicable to the unambiguous synthesis of quinoxalin-2-ones.[23-26] It involves the intermediate preparation of a 1,2,3,4-tetrahydro-2-oxoquinoxaline by the reductive ring closure of the *o*-nitrophenyl derivative of an α-aminoacid. These derivatives are formed readily from the aminoacid and an *o*-nitrohalogenobenzene. The final step of oxidation of the tetrahydro- to the dihydro-quinoxaline is carried out with potassium permanganate or hydrogen peroxide. The preparation of 7-nitroquinoxalin-2-one illustrates the application of this synthesis:



II. General Reactions

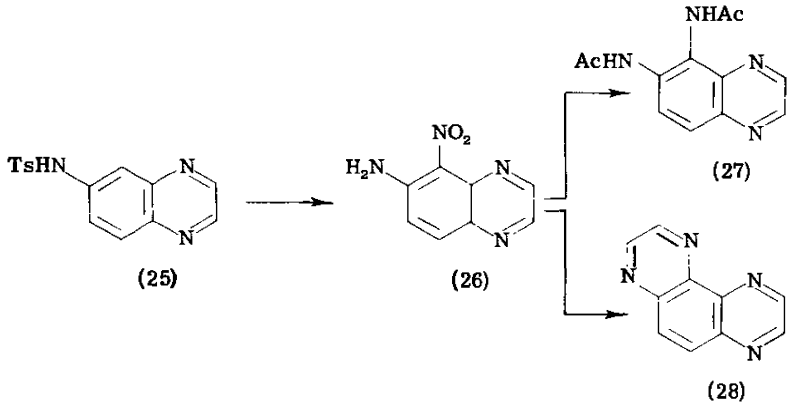
A. NUCLEAR SUBSTITUTION

1. *Electrophilic and Free Radical Substitution Reactions*

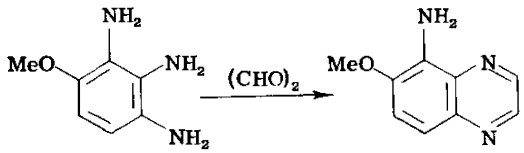
Quinoxaline is resistant to nitration under mild conditions. On treatment with a mixture of oleum and nitric acid at 90°C for 24

[22] T. S. Osdene and G. M. Timmis, *J. Chem. Soc.* pp. 2027, 4349 (1955).
[23] L. Horner, U. Schwenk, and E. Junghanns, *Ann.* **579**, 212 (1953).
[24] R. Van Dusen and H. P. Schultz, *J. Org. Chem.* **21**, 1326 (1956).
[25] E. Scoffoni, E. Vianello, and A. Lorenzini, *Gazz. chim. ital.* **87**, 354 (1957).
[26] M. Jutisz and W. Ritschard, *Biochim. et Biophys. Acta* **17**, 548 (1955).

hr it gives 1.5% of 5-nitroquinoxaline and 24% of 5,6-dinitroquinoxaline.[27] Reductive acetylation of the dinitro compound furnishes 5,6-diacetamidoquinoxaline (**27**) the structure of which has been confirmed by alternative synthesis from 6-toluene-*p*-sulfonamidoquinoxaline (**25**).[28] Nitration of (**25**) in glacial acetic acid gives the 5-nitro derivative and this on hydrolysis yields 6-amino-5-nitroquinoxaline (**26**). Deamination of (**26**) gives 5-nitroquinoxaline and reductive acetylation furnishes 5,6-diacetamidoquinoxaline (**27**). Reduction of 6-amino-5-nitroquinoxaline with stannous chloride and hydrochloric acid gives 5,6-diaminoquinoxaline which condenses with glyoxal–sodium bisulfite to give 4,7-diaza-1,10-phenanthroline (**28**).



The nitration of 6-methoxyquinoxaline in concentrated sulfuric acid at 0°C gives 6-methoxy-5-nitroquinoxaline. The position of the nitro group is confirmed by reduction of the product to 5-amino-6-methoxyquinoxaline identical with a sample prepared from 2,3,4-triaminoanisole and glyoxal:[29]



[27] M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* p. 2518 (1957).
[28] F. H. Case and J. A. Brennan, *J. Am. Chem. Soc.* **81**, 6297 (1959).
[29] Hirotaka Otomasu and Shoichi Nakajima, *Chem. & Pharm. Bull.* (*Tokyo*) **6**, 566 (1958); *Chem. Abstr.* **53**, 10243 (1959).

Nitration of 5-methoxyquinoxaline furnishes a dinitro derivative, presumably 5-methoxy-6,8-dinitroquinoxaline, but no mononitro derivative could be isolated.[29]

The bromination of 5,8-dimethoxyquinoxaline in methanol gives a mixture of 6-bromo and 6,7-dibromo compounds.[30] Treatment of 2-methylquinoxaline with bromine in acetic acid yields a mixture of 27% of 2-bromomethyl- and 37% of 2-dibromomethyl-quinoxaline.[31] Thus in the absence of powerfully activating groups, side-chain rather than nuclear substitution takes place.

A careful study of the phenylation of quinoxaline with benzoyl peroxide, various benzenediazonium salts, and *N*-nitrosoacetanilide indicates that the 2-position is most reactive to phenyl radicals and that the 5-position is more reactive than the 6. The yields of 2-, 5-, and 6-phenylquinoxaline are in the ratio of 40:10:1. Benzoyl peroxide and *N*-nitrosoacetanilide are the most effective phenylating reagents.[32]

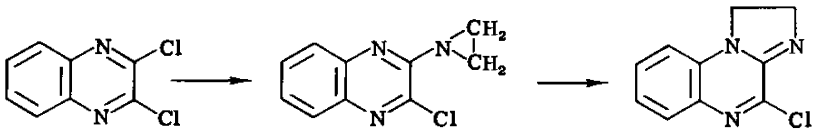
2. *Nuclear Displacement Reactions of α-Chloroquinoxalines*

Kinetic studies have been carried out on the displacement reactions of various chloroazanaphthalenes with ethoxide ions and piperidine.[33,34] 2-Chloroquinoxaline is even more reactive than 2-chloroquinazoline, thus demonstrating the powerfully electrophilic nature of the α-carbon atoms in the quinoxaline nucleus. The ease of displacement of α-chlorine in the quinoxaline series is of preparative value; thus, 2-alkoxy-,[35] 2-amino-,[35] 2-methylamino-,[36] 2-dimethylamino-,[36] 2-benzylamino-,[36] 2-mercapto-quinoxalines[37] are all readily prepared from 2-chloroquinoxaline. The anions derived from substituted acetonitriles have also been used to displace chloride ion from 2-chloroquinoxaline.[38]

The displacement of the two α-chloro atoms of 2,3-dichloroquinoxalines may be carried out in a stepwise manner (Scheme 3). Thus 2,3-dichloroquinoxaline has been converted into 2-amino-, 2-anilino-,

[31] Jiro Adachi, *Nippon Kagaku Zasshi* **76**, 311 (1955); *Chem. Abstr.* **51**, 17936 (1957).
[31] A. S. Elina, *J. Gen. Chem. USSR. (Eng. Transl.)* **29**, 2728 (1959).
[32] C. M. Atkinson and C. J. Sharpe, *J. Chem. Soc.* p. 3040 (1959).
[33] N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.* p. 1563 (1956).
[34] K. R. Brower, J. W. Way, W. P. Samuels, and E. D. Amstutz, *J. Org. Chem.* **19**, 1830 (1954).
[35] A. H. Gowenlock, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.* p. 622 (1945).
[36] G. W. H. Cheeseman, *J. Chem. Soc.* p. 3236 (1957).
[37] F. J. Wolf, R. M. Wilson, and M. Tishler, *J. Am. Chem. Soc.* **76**, 2266 (1954).
[38] R. N. Castle, A. Aldous, and C. Moore, *J. Org. Chem.* **21**, 139 (1956).

and 2-phenoxy-3-chloroquinoxaline.[38a] Reaction with aziridine furnishes 2-(1-aziridinyl)-3-chloroquinoxaline which on rearrangement gives 1,2-dihydro-4-chloroimidazo(1,2-a)quinoxaline.[38b]



Scheme 3

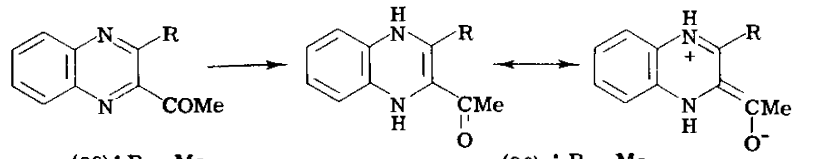
B. Addition to the N=C Function

Quinoxalines undergo facile addition reactions with nucleophilic reagents. The reaction of quinoxaline with allylmagnesium bromide gives, after hydrolysis of the initial adduct, 86% of 2,3-diallyl-1,2,3,4-tetrahydroquinoxaline. Quinoxaline is more reactive to this nucleophile than related aza-heterocyclic compounds, and the observed order of reactivity is pyridine < quinoline ≃ isoquinoline < phenanthridine ≃ acridine < quinoxaline.[39]

C. Reduction

1. *Dihydroquinoxalines*

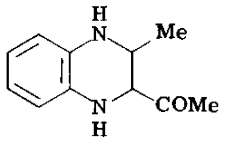
Catalytic reduction of 2-acetyl-3-methylquinoxaline (**29**) in ethanol with 1 mole of hydrogen, gives a deep crimson solution, from which red-brown needles of 2-acetyl-1,4-dihydro-3-methylquinoxaline (**30**) are obtained. Ethanolic solutions of (**30**) reoxidize on exposure to air to 2-acetyl-3-methylquinoxaline, but the solid dye is stable in air for several days. Similar results are obtained with 2-acetyl-3-phenylquinoxaline (**31**), from the reduction of which a purple-red dye (**32**) is obtained.[40]



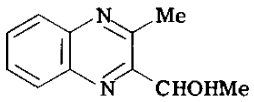
(29) : R = Me (30) : R = Me
(31) : R = Ph (32) : R = Ph

[38a] W. Deuschel and G. Riedel, *Ger. Patent* 1,135,471; *Chem. Abstr.* **58**, 537 (1963).
[38b] H. W. Heine and A. C. Brooker, *J. Org. Chem.* **27**, 2943 (1962).
[39] H. Gilman, J. Eisch, and T. Soddy, *J. Am. Chem. Soc.* **79**, 1245 (1957).
[40] J. A. Barltrop, C. G. Richards, and D. M. Russell, *J. Chem. Soc.* p. 1423 (1959).

In boiling ethanol, under nitrogen and in the presence of palladized charcoal, 2-acetyl-1,4-dihydro-3-methylquinoxaline (**30**) undergoes dismutation to give a mixture of 2-acetyl-3-methylquinoxaline, 2-acetyl-1,2,3,4-tetrahydro-3-methylquinoxaline (**33**), and 2-1′-hydroxyethyl-3-methylquinoxaline (**34**). The latter compound is the product of sodium borohydride or Meerwein-Ponndorf[41] reduction of 2-acetyl-3-methylquinoxaline.



(33)



(34)

Attempts to isolate 1,4-dihydroquinoxaline itself were not successful, but the polarographic behavior of quinoxaline and 6-substituted quinoxalines in buffered aqueous media suggests that in all cases reduction stops at the 1,4-dihydro stage.[42,43] 2,3-Dimethylquinoxaline and 2-D-*arabo*-tetrahydroxybutylquinoxaline show similar polarographic behavior.[44]

2. *Tetrahydroquinoxalines*

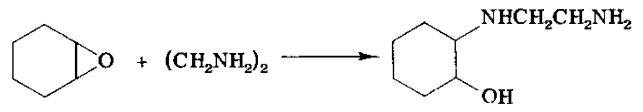
1,2,3,4-Tetrahydro derivatives are formed when either quinoxaline or 6-chloroquinoxaline is reduced with lithium aluminum hydride in ethereal solution.[45] Similar reduction of 2,3-dimethylquinoxaline gives the *meso*-(*cis*)-1,2,3,4-tetrahydro derivative. This is shown to be a stereospecific reduction since lithium aluminum hydride does not isomerize the *dl*-(*trans*)-compound. Low temperature, platinum catalyzed, hydrogenation of 2,3-dimethylquinoxaline in benzene also gives *meso*-(*cis*)-1,2,3,4-tetrahydro-2,3-dimethylquinoxaline.[46]

3. *Decahydroquinoxalines*

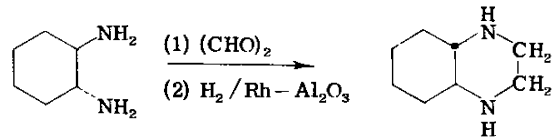
Hydrogenation of quinoxaline, or 1,2,3,4-tetrahydroquinoxaline, over a 5% rhodium-on-alumina catalyst at 100°C and 136 atm, or over

[41] W. H. Stafford, D. H. Reid, and P. Barker, *Chem. & Ind. (London)* p. 765 (1956).
[42] G. Sartori and C. Furlani, *Ann. chim. (Rome)* **45**, 251 (1955).
[43] M. P. Strier and J. C. Cavagnol, *J. Am. Chem. Soc.* **79**, 4331 (1957); *ibid.* **80**, 1565 (1958).
[44] C. Furlani, *Gazz. chim. ital.* **85**, 1668 (1955).
[45] R. F. Smith, W. J. Rebel, and T. N. Beach, *J. Org. Chem.* **24**, 205 (1959).
[46] R. C. De Selms and H. S. Mosher, *J. Am. Chem. Soc.* **82**, 3762 (1960).

freshly prepared Raney nickel W-6 under similar conditions, gives *meso*-(*cis*)-decahydroquinoxaline, mp 56–58°C, in high yield.[47] The decahydroquinoxaline, mp 150–151°C,[48] prepared by the action of ethylenediamine on cyclohexene oxide (**35**) and catalytic dehydrative ring closure of the product, is shown to be *dl*-(*trans*)-decahydroquinoxaline (**36**) by its alternative synthesis from *trans*-1,2-diaminocyclohexane (**37**). Attempts to resolve *dl*-(*trans*)-decahydroquinoxaline were unsuccessful.[17] (However, see addendum.) Hydrogenation of quinoxaline over a palladium-on-charcoal catalyst at 180°C and 50 atm gives *dl*-(*trans*)-decahydroquinoxaline; similar hydrogenation of 2-methylquinoxaline at 160°C and 50 atm gives a decahydro derivative. No decahydro derivatives were isolated from the hydrogenation of 2,3-dimethyl- and 2,3-diphenyl-quinoxaline under similar conditions, though at 20°C and 50 atm 1,2,3,4-tetrahydro derivatives were formed.[49]



(35)



(37) (36)

D. Oxidation

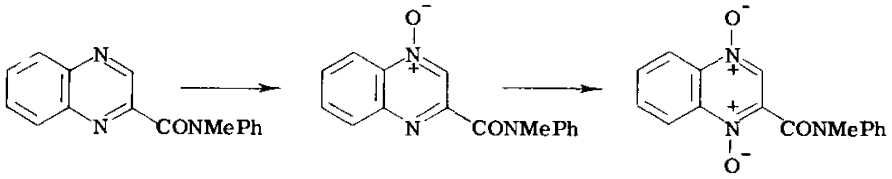
1. *N-Oxide Formation*

In the preparation of quinoxaline *N*-oxides, it is advantageous to use peracetic acid rather than aqueous hydrogen peroxide as the

[47] H. Smith Broadbent, E. L. Allred, L. Pendleton, and C. W. Whittle, *J. Am. Chem. Soc.* **82**, 189 (1960).
[48] R. M. Beck, K. E. Hamlin, and A. W. Weston, *J. Am. Chem. Soc.* **74**, 605 (1952).
[49] S. Maffei and S. Pietra, *Gazz. chim. ital.* **88**, 556 (1958).

oxidizing agent. Thus treatment of quinoxaline with 1 equivalent of peracetic acid in acetic acid gives quinoxaline 1-oxide, and with excess of peracetic acid quinoxaline 1,4-dioxide is formed.[50] Reaction of quinoxaline with 30% aqueous hydrogen peroxide in acetic acid, however, gives quinoxaline-2,3-dione (2,3-dihydroxyquinoxaline) as the main product.[51]

Substituents in the 2-position generally inhibit 1-oxide formation; for example, oxidation of 2-alkoxy-[10] and 2-carbethoxy-quinoxalines[52] furnishes the 4-oxides. Treatment of quinoxaline 2-carboxy-*N*-methylanilide (**38**) with 1 mole of peracetic acid gives the 4-oxide (**39**), and oxidation with excess of peracetic acid the 1,4-dioxide (**40**).[53]



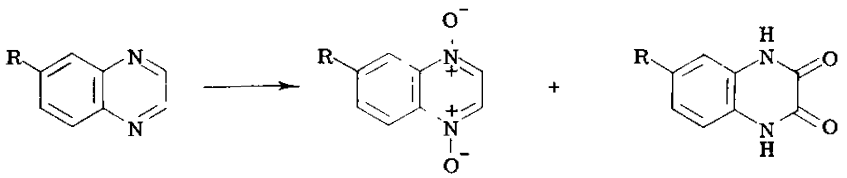
(38) (39) (40)

Reaction of 2,3-diphenylquinoxaline with excess of aqueous hydrogen peroxide in acetic acid gives, in addition to the expected 1,4-dioxide, *NN'*-dibenzoyl-*o*-phenylenediamine.[54]

5-Substituted quinoxalines afford mono-*N*-oxides, presumably the 1-oxides, and are resistant to further oxidation, though 5-methoxyquinoxaline is exceptional in forming a 1,4-dioxide. In the case of 6-substituted quinoxalines, as the substituent becomes more electron attracting, the yields of 1,4-dioxide decrease but more of the corresponding 2,3-dioxo compound (**41**) is formed.[50,55]

Peracetic acid oxidation of 1-methylquinoxalin-2-one (**42**) at 55°C gives 1-methylquinoxaline-2,3-dione (**43**) in moderate yield, and similar treatment of 1,3-dimethylquinoxalin-2-one (**44**) yields a small quantity of the 4-oxide.[56] An improved yield of (**43**) is obtained by

[50] J. K. Landquist, *J. Chem. Soc.* p. 2816 (1953).
[51] Motoji Asai, *Yakugaku Zasshi* **79**, 260 (1959); *Chem. Abstr.* **53**, 13160 (1959).
[52] A. S. Elina and O. Yu Magidson, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*) **25**, 145 (1955).
[53] M. S. Habib and C. W. Rees, *J. Chem. Soc.* p. 3386 (1960).
[54] E. Grovenstein, W. Postman, and J. W. Taylor, *J. Org. Chem.* **25**, 68 (1960).
[55] J. A. Silk, *J. Chem. Soc.* p. 2058 (1956).
[56] J. K. Landquist, *J. Chem. Soc.* p. 2830 (1953).



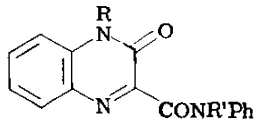
(41)

treatment of (**42**) with aqueous hydrogen peroxide at room temperature.[10]

(42) : R = H
(44) : R = Me

(43)

Oxidation of 4-methylquinoxalin-3-one-2-carboxy-*N*-methylanilide (**45**) with hydrogen peroxide and acetic acid furnishes the 1-oxide[57] but, on removal of either or both of the *N*-methyl groups (giving **46**, **47**, or **48**), oxidation with hydrogen peroxide or with peracetic or perbenzoic acid results in the removal of the carboxyamide groups and the formation of a quinoxaline-2,3-dione.[53]

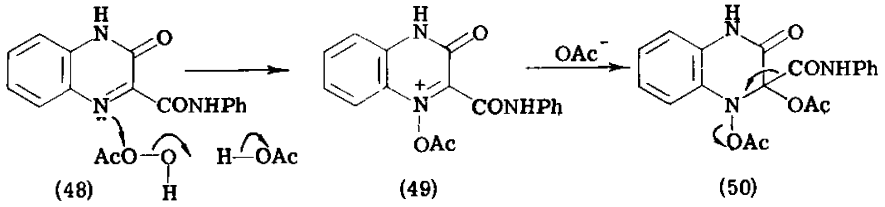


(45) : R = R' = Me
(46) : R = H, R' = Me
(47) : R = Me, R' = H
(48) : R = R' = H.

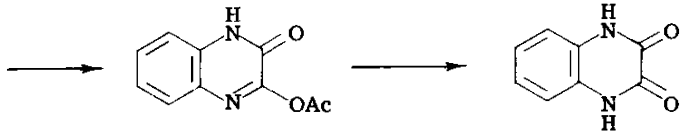
The mechanism proposed for this abnormal reaction is illustrated by reference to the conversion of quinoxalin-3-one-2-carboxyanilide (**48**)

[57] J. W. Clark-Lewis, *J. Chem. Soc.* p. 439 (1957).

into quinoxaline-2,3-dione (52). Hydrolysis of the *N*-acetoxy derivative (49) would yield the 1-oxide, acetic acid, and hydrogen ion in the usual manner, but reaction with acetate ion is facilitated by the electrophilic nature of carbon-2. Subsequent elimination from (50) gives the unstable acetyl derivative (51) and this on hydrolysis furnishes quinoxaline-2,3-dione (52).



(48) (49) (50)



(51) (52)

A novel synthesis of 2-aminoquinoxalin-3-one 1-oxide has been effected by the hydrogenation of *o*-nitro-1-cyanoformanilide in ethanol in the presence of Adam's catalyst.[57a]

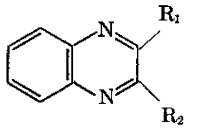
2. *Oxidation of Quinoxalines to Pyrazine-2,3-dicarboxylic Acids*

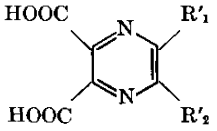
The electrolytic oxidation of quinoxaline at a copper anode gives pyrazine-2,3-dicarboxylic acid in excellent yield.[58] A similar conversion may be effected with alkaline potassium permanganate, and a list of quinoxaline derivatives which can be oxidized with potassium

[57a] C. W. Jefford, Ph.D. Dissertation, Princeton University, New Jersey, 1962.
[58] Takeshi Kimura, Shunichi Yamada, Keiro Yoshizue, and Tsutomu Nagoka, *Yakugaku Zasshi* **77**, 891 (1957); *Chem. Abstr.* **52**, 1181 (1958).

permanganate in water or dilute alkali is given in Table I. 2,3-Dialkoxy- and 2,3-diaryloxy-quinoxalines are stable toward potassium permanganate under the usual conditions.[59]

TABLE I
QUINOXALINE DERIVATIVES WHICH CAN BE OXIDIZED TO PYRAZINE-2,3-DICARBOXYLIC ACIDS ON A PREPARATIVE SCALE





R_1	R_2	R'_1	R'_2
H	H	H	H
COOH	COOH	COOH	COOH
$(CHOH)_3CH_2OH$	H	COOH	H
CH_3	H	CH_3	H
CH_3	CH_3	CH_3	CH_3
Cl	Cl	Cl(OH)	Cl(OH)

E. Quinoxaline Quaternary Salts

The formation of quinoxaline quaternary salts is often difficult. However, reaction of quinoxaline with ethyl iodide in boiling acetonitrile gives ethyl quinoxalinium iodide in 76% yield, and treatment of the parent base with methyl toluene-*p*-sulfonate at room temperature gives methyl quinoxalinium toluene-*p*-sulfonate in quantitative yield.[45]

III. Properties and Reactions of Some α-Substituted Quinoxalines

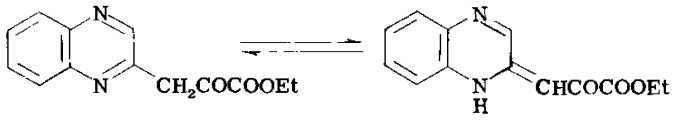
Only α-substituted quinoxalines are discussed because the reactions of 5- and 6-substituted quinoxalines are similar to those of the corresponding benzene derivatives.

A. Reactivity of α-Methyl Groups

α-Methylquinoxalines show the reactivity typical of active methyl compounds. For example, 2-methylquinoxaline undergoes numerous condensation reactions with aromatic and heterocyclic aldehydes,[60]

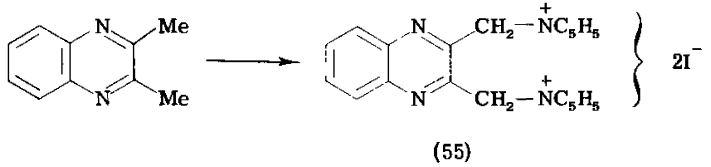
[59] H. I. X. Magner and W. Berends, *Rec. trav. chim.* **78**, 5 (1959).
[60] W. Ried and S. Hinschung, *Ann.* **600**, 47 (1956).

side-chain bromination (see Section II,A), and base-catalyzed Claisen condensation with esters. The tautomerism of ethyl 2-quinoxalinylpyruvate (**53**), prepared by condensation of 2-methylquinoxaline and diethyl oxalate, and related pyruvate esters has been investigated. The preferred tautomer is thought to be (**54**).[61]

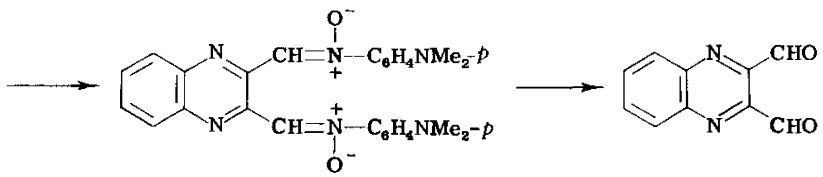


(53) (54)

2,3-Dimethylquinoxaline reacts with pyridine and iodine to form quinoxaline-2,3-bis(methylenepyridinium iodide) (**55**). Condensation of (**55**) with *p*-nitrosodimethylaniline in the presence of potassium carbonate yields the bis-(*p*-dimethylaminonitrone) (**56**) and this on acid hydrolysis gives quinoxaline 2,3-dialdehyde (**57**) in high over-all yield. The dialdehyde is also obtained by selenium dioxide oxidation of 2,3-dimethylquinoxaline.[62]



(55)



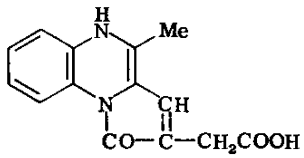
(56) (57)

2,3-Dimethylquinoxaline undergoes reaction with typical dienophiles such as maleic anhydride, *p*-benzoquinone, and *N*-phenylmaleimide. The products were formulated as Diels-Alder adducts primarily since analogous products were not isolated from reactions with other quinoxalines in which there was no possibility of tautomerism to a buta-1,3-diene system as (**58**).[63,64]

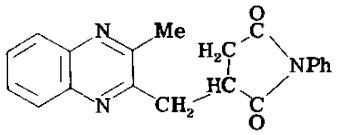
[61] A. M. Stock, W. E. Donahue, and E. D. Amstutz, *J. Org. Chem.* **23**, 1840 (1958).
[62] G. Henseke and K. J. Bähner, *Chem. Ber.* **91**, 1605 (1958).

(58)

Revised structures have been proposed for these compounds. The brownish-yellow acid obtained with maleic anhydride has been shown by ultraviolet, infrared, and nuclear magnetic resonance absorption measurements and oxidative degradation to have the tricyclic structure (**59**).[65] The "benzoquinone adduct" is a 2:1 molecular complex of 2,3-dimethylquinoxaline and quinol, and is readily prepared by crystallizing quinol from toluene in the presence of excess of 2,3-dimethylquinoxaline. 2,3-Dimethylquinoxaline and *N*-phenylmaleimide undergo Michael addition to form the quinoxalinylmethyl-*N*-phenylsuccinimide (**60**). 2-Methylquinoxaline, 2-methylquinoline, and 2-methylpyridine



(59)



(60)

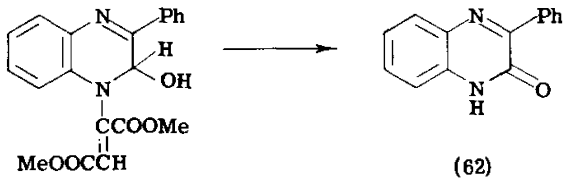
form similar adducts thus demonstrating that the possibility of tautomerism to a cyclic buta-1,3-diene is not a structural prerequisite for addition.[65a,65b]

B. Reaction of 2-Phenyl- and 2,3-Diphenyl-quinoxaline with Dimethyl Acetylenedicarboxylate

2-Phenylquinoxaline reacts with dimethyl acetylenedicarboxylate to give a product which after exposure to the atmosphere is isolated

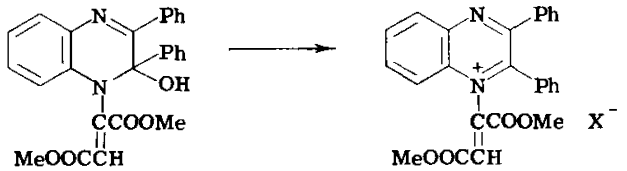
[63] A. Schönberg and A. Mustafa, *J. Chem. Soc.* p. 654 (1943).
[64] A. Mustafa and M. Kamel, *J. Am. Chem. Soc.* **77**, 1828 (1956).
[65] E. C. Taylor and E. S. Hand, *J. Am. Chem. Soc.* **85**, 770 (1963).
[65a] C. W. Bird and G. W. H. Cheeseman, *J. Chem. Soc.* p. 3037 (1962).
[65b] E. C. Taylor and E. S. Hand, *J. Org. Chem.* **27**, 3734 (1962).

as (**61**) and which on oxidation with potassium permanganate gives 3-phenylquinoxalin-2-one (**62**).



(61) (62)

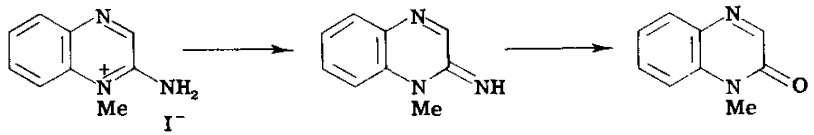
2,3-Diphenylquinoxaline reacts with dimethyl acetylenedicarboxylate in methanol to give a yellow adduct which consists of 1 mole of each of the reactants and to which is assigned an analogous structure (**63**). In acidic methanol the adduct forms salts of the type (**64**).[54]



(63) (64)

C. Quaternization of 2-Amino- and 2-Acetamido-quinoxaline

2-Aminoquinoxaline 1-methiodide (**65**) is slowly formed when 2-aminoquinoxaline is treated with excess of methyl iodide in methanol at room temperature. Decomposition of the 1-methiodide with cold aqueous sodium hydroxide solution gives 1-methylquinoxalin-2-one-imine (**66**) and this on hydrolysis yields 1-methylquinoxalin-2-one.[66]

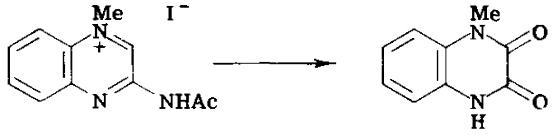


(65) (66)

Treatment of 2-aminoquinoxaline with methyl toluene-*p*-sulfonate at

[66] G. W. H. Cheeseman, unpublished work.

105°C and addition of excess of potassium iodide to the product, gives only a small yield of methiodide, but 2-acetamidoquinoxaline 4-methiodide (**67**) is readily prepared by this method. Proof that quaternization occurs at position 4 is obtained by degradation of (**67**) by boiling alkali to 1-methylquinoxaline-2,3-dione and 1 equivalent of ammonia. Similar treatment of the 1-methiodide would yield 1-methylquinoxalin-2-one, and under these conditions this compound is not converted into the dione.[9]



(67)

D. Tautomerism of 2-Aminoquinoxaline

2-Aminoquinoxaline exists predominantly as such rather than in the tautomeric imino form.[66] This is indicated by a comparison of the basic strength of the 2-amino compound (pK_a 3.90) and those of its fixed methylated tautomers, 2-dimethylaminoquinoxaline (pK_a 3.72) and 1-methylquinoxalin-2-oneimine (pK_a 8.70). The ultraviolet spectrum of the neutral molecule of 2-dimethylaminoquinoxaline shows the expected bathochromic shifts compared to that of 2-aminoquinoxaline[67]; these spectra differ from the ultraviolet spectrum of the neutral molecule of 1-methylquinoxalin-2-oneimine (Fig. 1). The mono-cations (**68**) and (**69**) derived from 2-aminoquinoxaline and 1-methylquinoxalin-2-oneimine have a similar chromophoric system and show almost identical ultraviolet absorption (Fig. 2).

(68) : R = H
(69) : R = Me

[67] G. W. H. Cheeseman, *J. Chem. Soc.* p. 108 (1958).

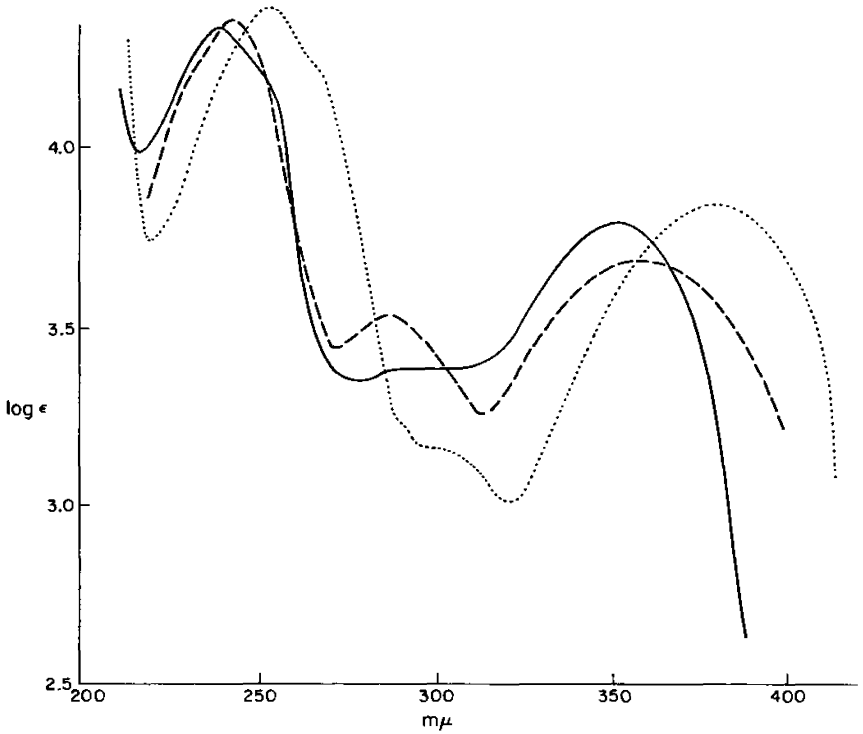


FIG. 1. Neutral molecules of 2-aminoquinoxaline (———), 1-methylquinoxalin-2-oneimine (------), and 2-dimethylaminoquinoxaline (.....).

E. REACTIONS OF QUINOXALIN-2-ONES AND QUINOXALINE-2,3-DIONES (2-HYDROXY- AND 2,3-DIHYDROXY-QUINOXALINES)[67a]

1. *Chlorination*

Quinoxalin-2-ones are readily converted into the corresponding 2-chloroquinoxalines by treatment with phosphoryl chloride; in the case of the highly insoluble 2,3-diones chlorination is effected conveniently with a mixture of phosphoryl chloride and dimethylaniline.[50,68] The use of phosphorus pentachloride may lead to side reactions, for example, quinoxalin-2-one (**70**) is converted into 2,3-

[67a] These compounds are also named 2(1*H*)-quinoxalinones and 2,3(1*H*,4*H*)-quinoxalinediones or 1,2-dihydro-2-oxo- and 1,2,3,4-tetrahydro-2,3-dioxo-quinoxalines.
[68] G. W. H. Cheeseman, *J. Chem. Soc.* p. 1170 (1962).

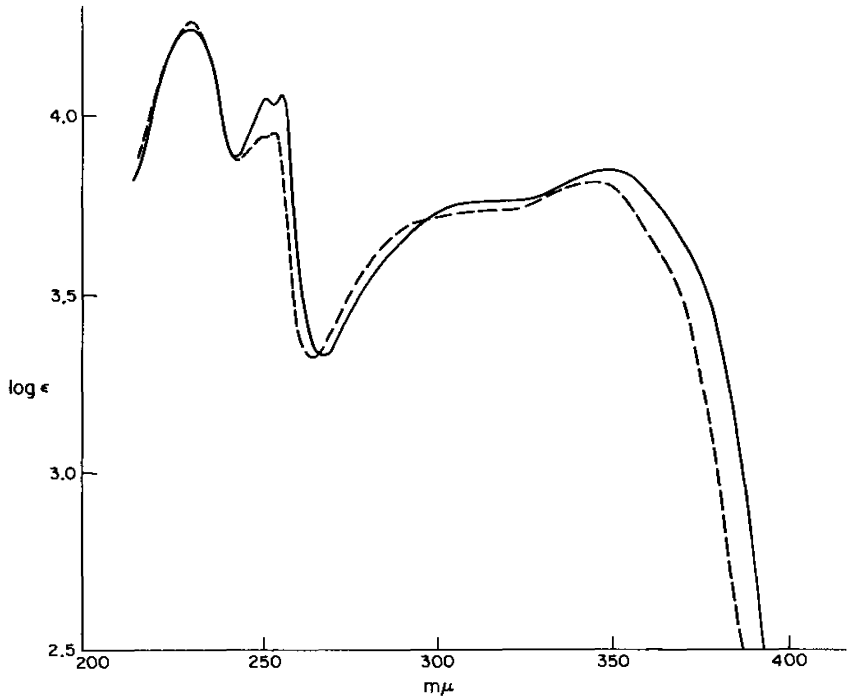


FIG. 2. Cations of 2-aminoquinoxaline (———) and 1-methylquinoxalin-2-oneimine (------).

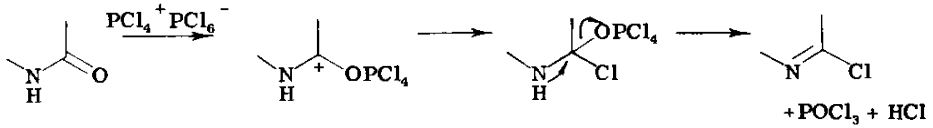
dichloroquinoxaline with this reagent.[1] α-Chloroquinoxalines, as already indicated, undergo facile displacement reactions with nucleophilic reagents, and so the readily available quinoxalin-2-ones are useful intermediates in quinoxaline synthesis.

Quinoxalin-2-one (**70**) is in mobile tautomeric equilibrium with 2-hydroxyquinoxaline (**71**), but physical measurements fail to demonstrate the presence of the hydroxy form (see following).

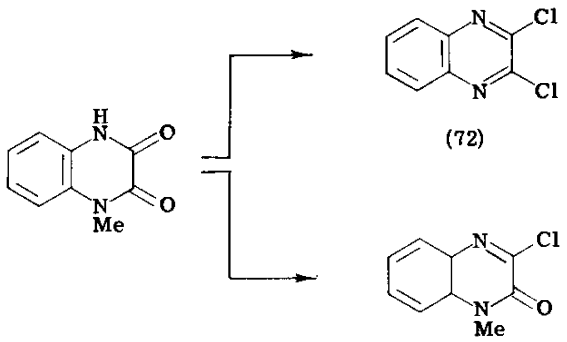
(70) (71)

The ready conversion of quinoxalin-2-ones into 2-chloroquinoxalines is not chemical evidence for the existence of the hydroxy form. Phen-

olic hydroxyl groups are difficult to replace with chlorine, and this reaction is more correctly regarded as the transformation of a secondary amide into the corresponding iminochloride. A general mechanism for this type of conversion is as follows:



The conversion —NMe—CO—→—N=CCl— may also be effected with phosphorus pentachloride. This occurs with elimination of methyl chloride and further emphasizes that formation of a chloro derivative is due to amide–carbonyl reactivity. Thus treatment of 1-methylquinoxaline-2,3-dione with phosphorus pentachloride gives 2,3-dichloroquinoxaline (**72**),[69] and with phosphoryl chloride, 3-chloro-1-methylquinoxalin-2-one (**73**) is formed.[70]



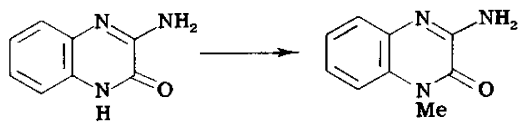
(72)

(73)

2. *Methylation*

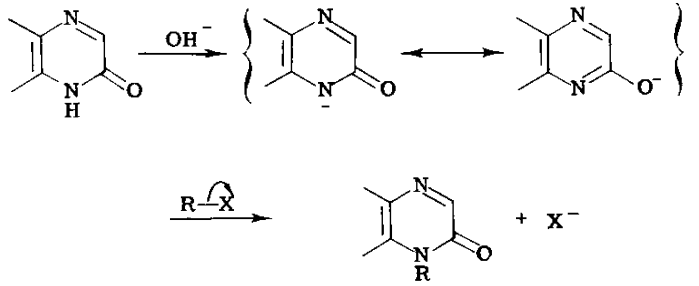
Treatment of an alkaline solution of quinoxalin-2-one or quinoxaline-2,3-dione with an alkyl iodide or sulfate results in *N*-methylation. Thus methylation of 3-aminoquinoxalin-2-one (**74**) with methyl sulfate and alkali gives 3-amino-1-methylquinoxalin-2-one (**75**) and not as previously reported the isomeric *O*-methyl derivative.[70]

[69] E. H. Usherwood and M. A. Whiteley, *J. Chem. Soc.* p. 1084 (1923).
[70] G. W. H. Cheeseman, *J. Chem. Soc.* p. 1804 (1955).



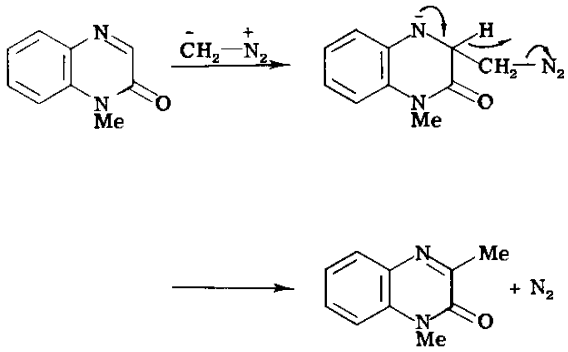
(74) (75)

It, therefore, appears that the preferred nucleophilic center in resonant anions of the type shown in Scheme 4 is nitrogen rather than oxygen.



SCHEME 4

With diazomethane, quinoxalin-2-ones and quinoxaline-2,3-diones form mixtures of *N*- and *O*-methyl derivatives. A consideration of the mechanisms of these reactions is complicated by the fact that diazomethane ($CH_2{=}\overset{+}{N}{=}\overset{-}{N} \leftrightarrow \overset{-}{C}H_2{-}\overset{+}{N}{\equiv}N$) may function as an electrophilic or nucleophilic reagent. However it is certainly an over-



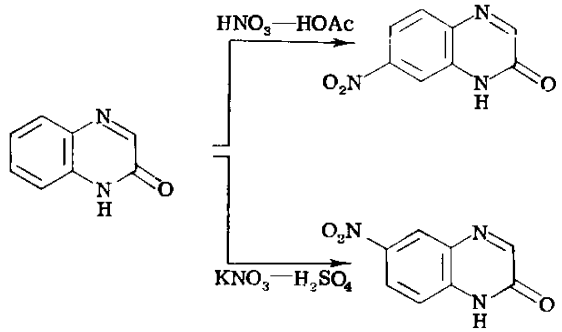
SCHEME 5

simplification to assume that the *N*-methyl derivative is formed necessarily from the cyclic amide form, e.g. (**70**), and the *O*-methyl derivative from the tautomeric hydroxy form, e.g. (**71**).

1-Methylquinoxalin-2-one is converted into 1,3-dimethylquinoxalin-2-one with diazomethane.[70] This unusual *C*-methylation is probably a result of the electrophilic character of carbon-3 in the monomethyl compound and may occur by the mechanism shown in Scheme 5. Reaction of an aqueous solution of either benzene- or *p*-nitrobenzenediazonium chloride with 1-methylquinoxalin-2-one results in arylation at position 3.[10]

3. *Nitration and Halogenation*

Quinoxalin-2-ones, unlike quinoxaline itself, may be nitrated under mild conditions.[29,71] Nitration of quinoxalin-2-one in acetic acid gives mainly the 7-nitro derivative; in sulfuric acid, the 6-nitro compound is formed (Scheme 6).[10]



SCHEME 6

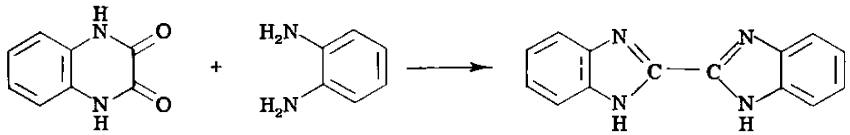
Quinoxalin-2-one is a very weak base (pK_a — 1.37) and so the different orientation of substitution in acetic and sulfuric acids may mean that in acetic acid the principal species undergoing nitration is the neutral molecule, and in sulfuric acid, the mono-cation. Treatment of quinoxaline-2,3-dione, or its *NN'*-dimethyl derivative in sulfuric acid, with 1 equivalent of potassium nitrate, results in nitration at position 6; with 2 equivalents of potassium nitrate, 6,7-dinitro compounds are formed.[68] When quinoxaline is boiled with aqueous nitric acid, 6-

[71] Kazuo Asano and Sotoo Asai, *Yakugaku Zasshi* **79**, 658 (1959); *Chem. Abstr.* **53**, 21979 (1959).

nitroquinoxaline-2,3-dione is obtained, presumably owing to oxidation and subsequent nitration.[51] Chlorination and bromination of quinoxaline-2,3-dione and its *NN'*-dimethyl derivative gives 6- and 6,7-substituted derivatives.[68] It, therefore, appears that substitution procedures offer a useful alternative to the classical quinoxaline synthesis, particularly when the required *o*-phenylenediamine is not readily available.

4. *Ring Cleavage of Quinoxaline-2,3-dione*

This occurs when the dione is boiled in ethylene glycol with *o*-phenylenediamine and with the formation of 2,2'-bisbenzimidazoyl (**76**) as the main product. The reaction between oxamide and



(**76**)

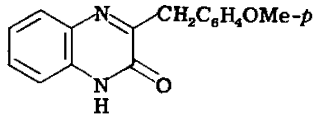
2 equivalents of *o*-phenylenediamine in ethyleneglycol also gives (**76**); under these conditions the initially formed quinoxaline-2,3-dione is converted into 2,2'-bisbenzimidazoyl.[72]

F. Tautomerism of Quinoxalin-2-ones and Quinoxaline-2,3-diones and of 5- and 6-Hydroxyquinoxalines

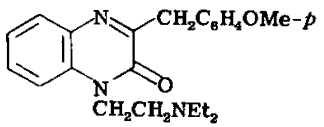
Quinoxalin-2-ones are in tautomeric equilibrium with 2-hydroxyquinoxalines, but physical measurements indicate that both in solution and in the solid state they exist as cyclic amides rather than as hydroxy compounds.[73] Thus quinoxalin-2-one and its *N*-methyl derivative show practically identical ultraviolet absorption and are bases of similar strength. In contrast, the ultraviolet spectra of quinoxalin-2-one and its *O*-methyl derivative (2-methoxyquinoxaline) are dissimilar. The methoxy compound is also a significantly stronger base (Table II). Similar relationships also exist between the ultraviolet absorption and ionization properties of 3-methylquinoxalin-2-one and its *N*- and *O*-methyl derivatives.[67] The infrared spectrum of 3-(*p*-methoxybenzyl)quinoxalin-2-one (**77**) in methylene chloride shows bands at 3375 and 1565 cm^{-1} which are absent in the spectrum of the deuterated

[72] E. S. Lane, *J. Chem. Soc.* p. 1079 (1955).
[73] S. F. Mason, *J. Chem. Soc.* pp. 4874, 5010 (1957); *ibid.* p. 674 (1958).

compound. These are, therefore, attributed to the NH group; the amide carbonyl band is at 1660 cm^{-1}. The ultraviolet spectra of (77) and its *N*-alkylated derivative (78) are closely similar and thus confirm that (77) exists as a cyclic amide.[74]

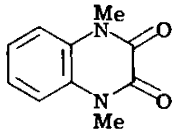


(77)

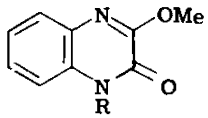


(78)

Ultraviolet[67] and infrared[75] spectroscopy indicate that quinoxaline-2,3-dione type structures are preferred to the tautomeric 3-hydroxyquinoxalin-2-one or 2,3-dihydroxyquinoxaline forms. The light absorption properties (UV) of quinoxaline-2,3-dione have been compared with those of its *NN'*-, *ON*-, and *OO'*-dimethyl derivatives (79, 80, and 81), and also its *N*- and *O*-monomethyl derivatives (43 and 82). The parent dicarbonyl compound and its mono- and di-*N*-methyl derivatives show very strong carbonyl absorption near to 1690 cm^{-1} split into two peaks.

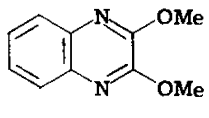


(79)



(80) : R = Me

(82) : R = H



(81)

5- and 6-Hydroxyquinoxalines are in potential tautomeric equilibrium with the amides (83 and 84), respectively, but exist predom-

(83)

[74] J. Derkosch, *Monatsh. Chem.* **92**, 1107 (1961).

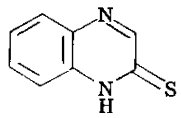
[75] G. W. H. Cheeseman, A. R. Katritzky, and S. Øksne, *J. Chem. Soc.* p. 3983 (1961).

(84)

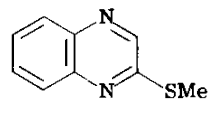
inantly as phenols rather than as cyclic vinylogous amides. The tautomerism of these compounds has been investigated by ionization and by ultraviolet and infrared measurements.[73] Thus 5- and 6-hydroxyquinoxalines are stronger bases and acids than quinoxalin-2-one (Table II, p. 241). The infrared spectrum of 5-hydroxyquinoxaline in carbon tetrachloride shows a broad band typical of an intramolecularly bonded hydroxyl group and that of 6-hydroxyquinoxaline a sharp band due to O—H stretching. Quinoxalin-2-one, however, shows bands attributable to NH and CO groups.

G. Reactions and Tautomerism of Quinoxaline-2-thione and Quinoxaline-2,3-dithione (2-Mercapto- and 2,3-Dimercapto-quinoxaline)

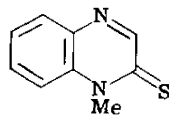
Treatment of quinoxaline-2-thione (85) with methyl iodide and alkali gives 2-methylthioquinoxaline (86) and apparently no 1-methylquinoxaline-2-thione (87). The latter compound is prepared conven-



(85)



(86)



(87)

iently by reaction of 1-methylquinoxalin-2-one with phosphorus pentasulfide in pyridine.[66] Quinoxaline-2-thione (85) must exist in solution as such rather than as 2-mercaptoquinoxaline because of the close similarity of its basic strength and ultraviolet absorption to that of its *N*-methyl derivative (87); compounds 85 and 87 differ in basic strength and in ultraviolet absorption to 2-methylthioquinoxaline (Table II and Fig. 3). A detailed investigation of the tautomeric equilibria of related heterocyclic thioamides by ionization and by ultraviolet and infrared measurements has revealed that thioamide, rather than the tautomeric α-mercapto, structures are preferred both

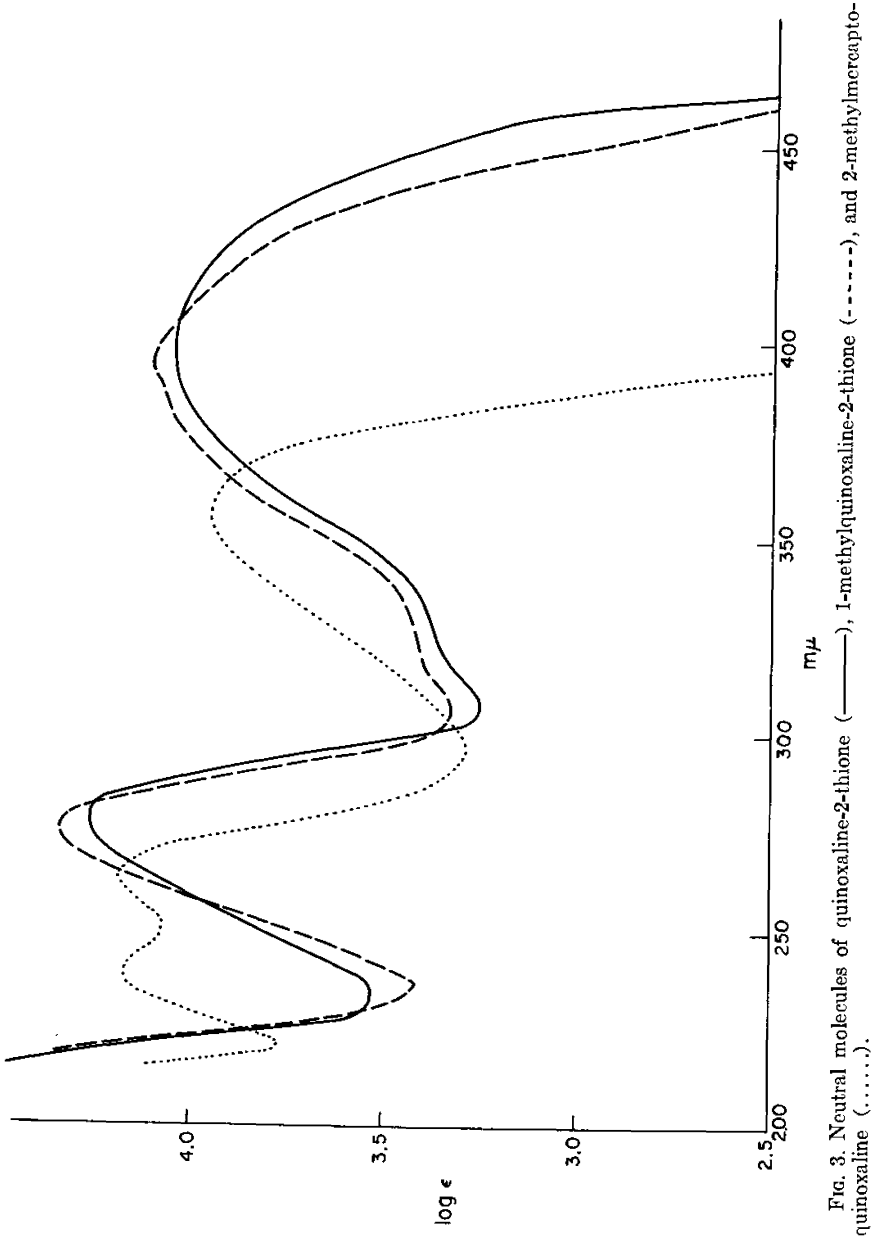
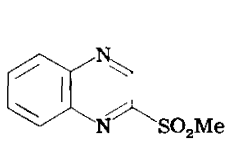


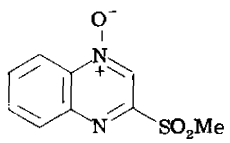
FIG. 3. Neutral molecules of quinoxaline-2-thione (——), 1-methylquinoxaline-2-thione (- - - - -), and 2-methylmercapto-quinoxaline (. . . . .).

in solution and in the solid state. A similar situation obtains in thioamides when the sulfur is γ to a ring nitrogen.[76,77]

2-Methylthioquinoxaline is oxidized by hydrogen peroxide in acetic acid at room temperature mainly to 2-methylsulfonylquinoxaline (**88**); at 55°C, 2-methylsulfonylquinoxaline 4-oxide (**89**) and quinoxaline-2,3-dione are formed.



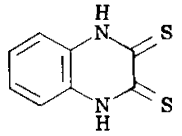
(88)



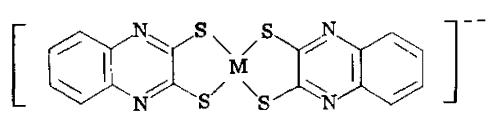
(89)

The methylsulfonyl group in (**88**) and (**89**) is very readily displaced by treatment with aqueous alkali.[36]

Quinoxaline-2,3-dithione (2,3-dimercaptoquinoxaline) (**90**) forms chelates with several transition elements[78] and is used as a colorimetric agent for the detection and quantitative estimation of nickel[79] and also for the quantitative estimation of palladium.[80] Nickel gives a pink coloration with (**90**) in ammoniacal solution, and palladium an orange-red color in *NN*-dimethylformamide solution containing a little hydrochloric acid. Spectrophotometric studies of the chelate compounds of (**90**) with Ni(II), Co(II), and Pd(II) in alkaline solu-



(90)



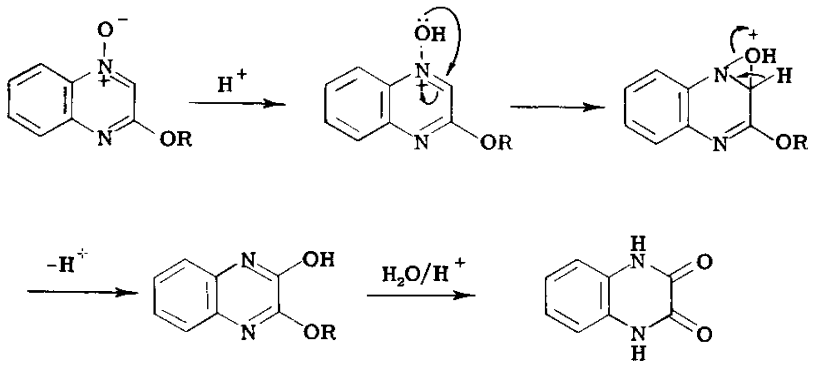
tion indicate a metal-quinoxaline ratio of 1:2.[81] The metal ions are covalently bonded to give complex anions of the type shown. In acidified aqueous dimethylformamide the reaction ratio of metal ion

[76] A. Albert and G. B. Barlin, *J. Chem. Soc.* p. 2384 (1959).
[77] E. Spinner, *J. Chem. Soc.* p. 1237 (1960).
[78] D. C. Morrison and A. Furst, *J. Org. Chem.* **21**, 470 (1956).
[79] D. A. Skoog, Ming-Gon Lai, and A. Furst, *Anal. Chem.* **30**, 365 (1958).
[80] G. H. Ayres and H. F. Janota, *Anal. Chem.* **31**, 1985 (1959).
[81] D. B. Stevencevic and V. G. Drazic, *Bull. Inst. Nuclear Sci. "Boris Kidrich" (Belgrade)* **9**, 69 (1959); *Chem. Abstr.* **53**, 20071 (1959).

to reagent varies from 1:2 to 1:2.5 for nickel and 1:4 to 1:5.5 for cobalt. Polymeric structures are suggested for these complexes, in which the polymeric chains consist of alternating metal ion and quinoxaline-2,3-dithione links.[81a] Treatment of quinoxaline-2,3-dithione with hydrazine hydrate at 100°C gives 3-hydrazino-quinoxaline-2-thione.[82] Numerous derivatives of this compound have been prepared and screened for antibacterial activity.[83] A new group of plant preservatives has been derived from quinoxaline-2,3-dithione and substituted 2,3-dithiones by reaction with carboxylic, carbonic, and inorganic acid derivatives, and with organometallic and geminal dihalogeno compounds.[84]

IV. Reactions of Quinoxaline *N*-Oxides

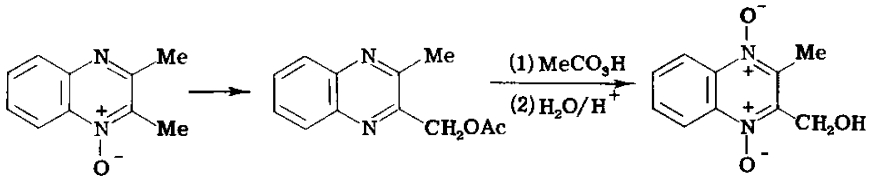
Quinoxaline *N*-oxides undergo rearrangement under a variety of conditions. Thus on treatment of 2-ethoxy-[85] and 2-methoxy-quinoxaline[10] 4-oxide with hydrochloric acid, rearrangement and hydrolysis occurs to give quinoxaline-2,3-dione. A possible intramolecular mechanism of rearrangement is shown in Scheme 7. Reaction of 2,3-



SCHEME 7

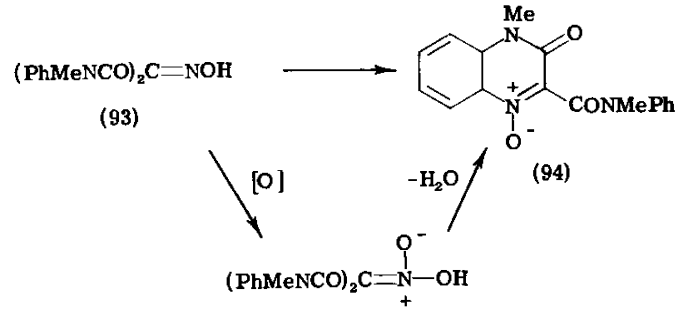
[81a] G. H. Ayres and R. H. Annand, *Anal. Chem.* **35**, 33 (1963).
[82] Kazuo Asano, Sotoo Asai and Naojuki Inoue, *Yakugaku Zasshi* **79**, 24, 368 (1959); *Chem. Abstr.* **53**, 10242, 13401 (1959).
[83] Kazuo Asano and Sotoo Asai, *Yakugaku Zasshi* **79**, 567, 661 (1959); *Chem. Abstr.* **53**, 21979 (1959).
[84] K. Sasse, R. Wegler, G. Unterstenhöfer, and F. Grewe, *Angew. Chem.* **72**, 973 (1960).
[85] G. T. Newbold and F. S. Spring, *J. Chem. Soc.* p. 519 (1948).

dimethylquinoxaline 1-oxide with acetic anhydride gives as expected 2-acetoxymethyl-3-methylquinoxaline (**91**) which can be transformed to the highly antibacterial 2-hydroxymethyl-3-methylquinoxaline 1,4-dioxide (**92**) as shown. Treatment of 2,3-dimethylquinoxaline 1,4-dioxide with acetic anhydride similarly furnishes 2,3-bis(acetoxymethyl)quinoxaline.[86] However, when quinoxaline 1,4-dioxide is treated with acetic anhydride, 2-acetoxyquinoxaline 1-oxide is formed. This on alkaline hydrolysis furnishes 2-hydroxyquinoxaline 1-oxide.[86a] The reactions of 2-phenylquinoxaline 4-oxide with reducing agents, sulfuryl chloride, acid chlorides and anhydrides, organometallic compounds, and a variety of other reagents have been reported.[86b]



(91) (92)

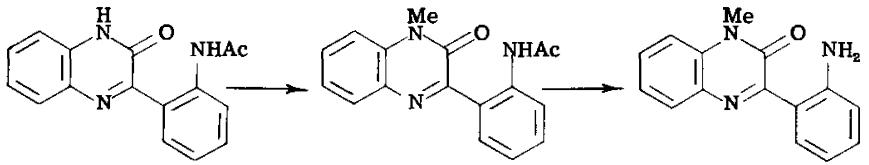
Chromic acid oxidation of hydroxyiminomalon-bis-*N*-methylanilide (**93**) gives 4-methylquinoxalin-3-one-2-carboxy-*N*-methylanilide 1-oxide (**94**) by a process involving *N*-oxidation and dehydrative ring closure.[69]



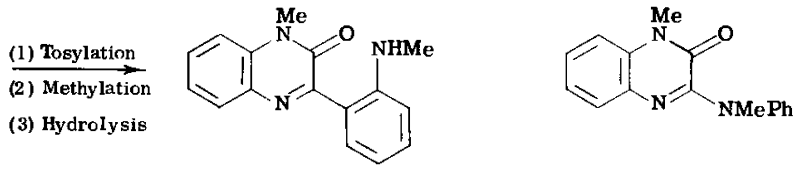
The structure of the latter compound has been confirmed by alternative synthesis from 4-methylquinoxalin-3-one-2-carboxylic acid, which

[86] A. S. Elina, J. Gen. Chem. U.S.S.R. (Eng. Transl.) **31**, 942 (1961).
[86a] A. S. Elina, *Zhur. Obshchei Khim.* **32**, 2967 (1962); *Index Chemicus*, No. 24471 (Jan. 15, 1963).
[86b] E. Hayashi and C. Iijima, *Yakugaku Zasshi* **82**, 1093 (1962); *Index Chemicus*, No. 23837 (Dec. 30, 1962).

after conversion into its *N*-methylanilide and subsequent oxidation in acetic acid with 30% hydrogen peroxide, gives the *N*-oxide (**94**). Treatment of this compound with concentrated sulfuric acid at 0°C results in rapid loss of carbon dioxide and formation of 1-methyl-3-*o*-methylaminophenylquinoxalin-2-one (**96**), and not the tertiary amine (**97**) as originally proposed.[57] The structure of (**96**) has been confirmed by synthesis from 3-*o*-acetamidophenylquinoxalin-2-one (**95**) as shown.

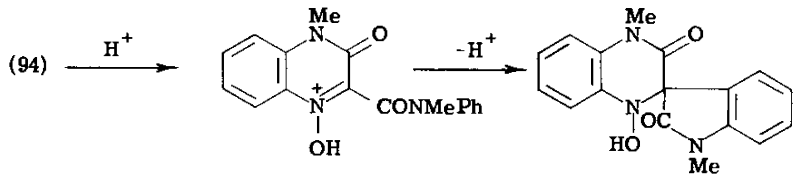


(95)

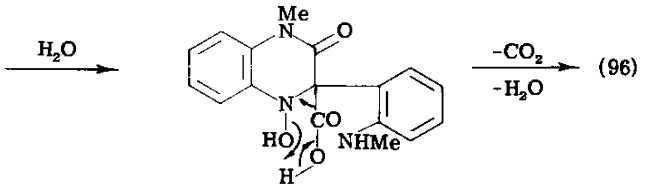


(96) (97)

The mechanism for the conversion of the *N*-oxide (**94**) to the *o*-methylaminophenylquinoxaline (**96**) involves an initial protonation of the *N*-oxide function. This enhances the electrophilic reactivity of the α-carbon atom which then effects an intramolecular electrophilic substitution at an *ortho* position of the anilide ring to give the spirolactam (**98**). Hydrolytic ring cleavage of (**98**) gives the acid (**99**), which undergoes ready dehydration and decarboxylation to (**96**), the availability of the cyclic transition state facilitating these processes.[5]

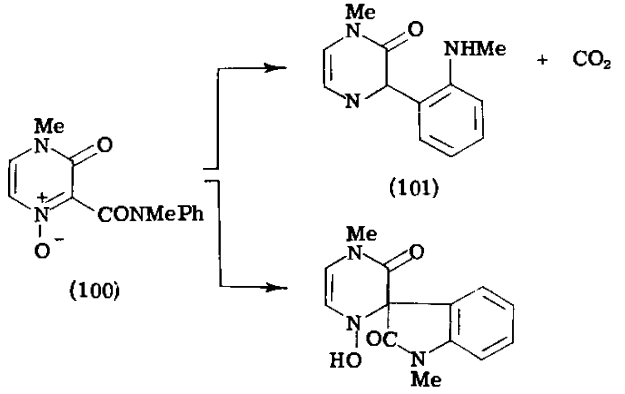


(98)



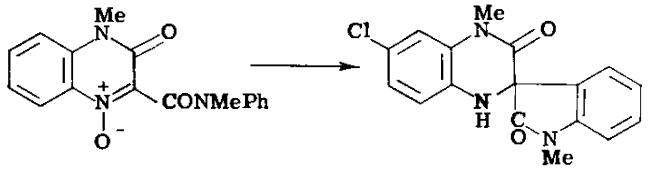
(99)

The pyrazine *N*-oxide (**100**) undergoes a similar reaction in sulfuric acid to give (**101**) but more vigorous conditions are required. In boiling ethanolic hydrogen chloride, (**100**) is converted into the pyrazine spirolactam (**102**), corresponding in structure to the highly labile quinoxaline spirolactam (**98**), postulated as an intermediate in the foregoing rearrangement.[87] Treatment of 4-methylquinoxalin-3-



(102)

one-2-carboxy-*N*-methylanilide 1-oxide with boiling ethanolic hydrogen chloride gives the spiro-6-chloroquinoxaline (**103**). Presumably

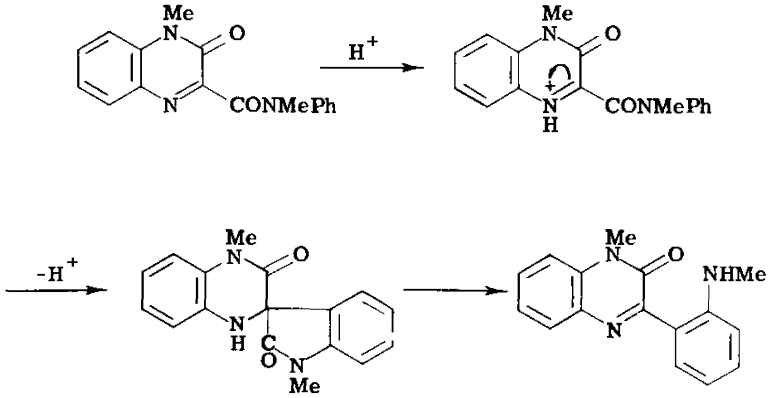


(103)

[87] M. S. Habib and C. W. Rees, *J. Chem. Soc.* p. 123 (1962).

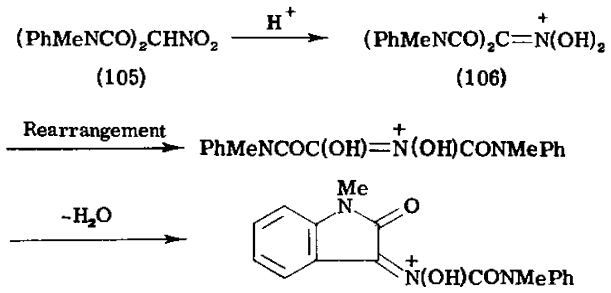
the quinoxaline-spirolactam (**98**) is formed as an intermediate and is transformed into (**103**) by a process analogous to the conversion of *N*-phenylhydroxylamine into *p*-chloroaniline.[4]

4-Methylquinoxalin-3-one-2-carboxy-*N*-methylanilide is unstable in concentrated sulfuric acid; at low temperatures it is converted in low yield into the spirolactam (**104**). An almost quantitative conversion is effected with boiling ethanolic hydrogen chloride. A similar mechanism for this rearrangement is proposed; treatment of (**104**) with boiling aqueous-ethanolic hydrochloric acid gives 1-methyl-3-*o*-methylaminophenylquinoxalin-2-one.[87]

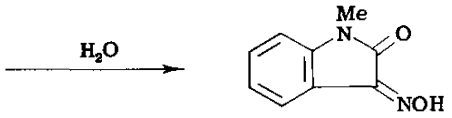


(104)

Reaction of nitromalon-bis-*N*-methylanilide (**105**) with sulfuric acid gives *N*-methylisatin-β-oxime (**107**) and not 4-methylquinoxalin-3-one 1-oxide (**108**) as originally suggested. This transformation may involve a Beckmann-type rearrangement of the protonated *aci*-nitro compound (**106**) prior to dehydrative ring closure.[4]

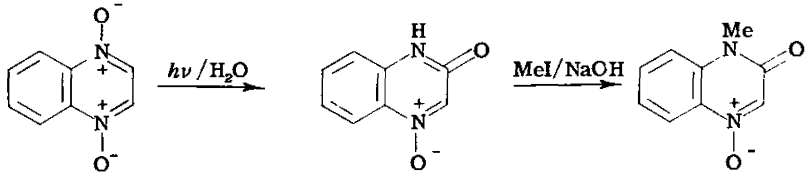


(105) (106)



(107)

The authentic quinoxaline *N*-oxide (**108**) is prepared from quinoxaline 1,4-dioxide by the following route[56]:

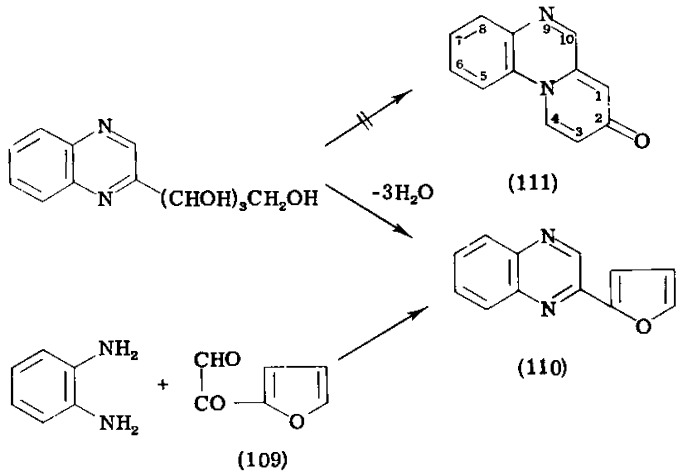


(108)

V. Miscellaneous Quinoxaline Derivatives

A. Reformulation of Glucazidone

The structure of glucazidone, obtained by treatment of 2-D-*arabo*-tetrahydroxybutylquinoxaline with sulfuric acid, is shown to be 2-(2′-furyl)quinoxaline (**110**), and not (**111**) as originally proposed. This follows from the synthesis of (**110**) from *o*-phenylenediamine and 2-furanglyoxal (**109**); "3-hydroxyglucazidone," obtained as a by-product in the preparation of glucazidone, is reformulated as 2-(3′-hydroxy-2′-

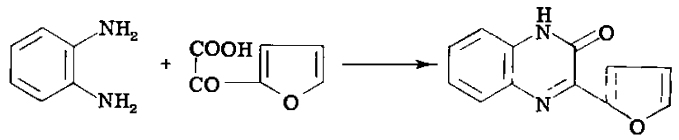


(111)

(110)

(109)

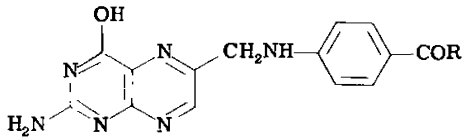
furyl)quinoxaline. "10-Hydroxyglucazidone," prepared by dehydration of 3-D-*arabo*-tetrahydroxybutylquinoxalin-2-one is shown to be 3-(2′-furyl)quinoxalin-2-one (**113**) by its synthesis from *o*-phenylenediamine and furanglyoxylic acid (**112**).[88,89]



(112) (113)

B. Quinoxaline Analogs of Pteroic Acid

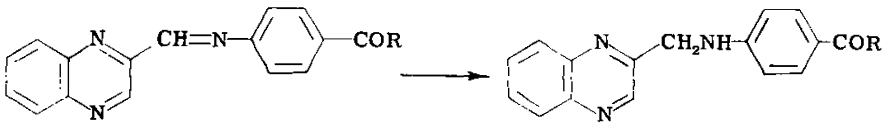
Several quinoxaline analogs of pteroic acid (**114**) and pteroylglutamic acid (**115**) have been prepared.[90-92] Quinoxaline-2-aldehyde,



(114) : R = OH

(115) : R = NHCH(COOH)CH_2CH_2COOH

conveniently obtained by oxidation of 2-D-*arabo*-tetrahydroxybutylquinoxaline with sodium metaperiodate, reacts with *p*-aminobenzoic acid, or its ethyl ester, to give the anils (**116** and **117**). Catalytic hydrogenation of **116** and **117** furnishes *N*-2′-quinoxalinylmethyl-*p*-aminobenzoic acid (**118**) and its ethyl ester (**119**), respectively.



(116) : R = OH (118) : R = OH

(117) : R = OEt (119) : R = OEt

[88] A. Gómez-Sánchez, M. Yruela-Antiñolo, and F. García González, *Anales real soc. españ. fís. y quím. (Madrid)* **50B**, 431 (1954); *Chem. Abstr.* **52**, 11078 (1958).

[89] A. Gómez-Sánchez and M. Yruela-Antiñolo, *Anales real soc. españ. fís. y quím. (Madrid)* **51B**, 423 (1955); *Chem. Abstr.* **50**, 10108 (1956).

[90] C. L. Leese and H. N. Rydon, *J. Chem. Soc.* p. 303 (1955).

[91] J. Drumheller and H. P. Schultz, *J. Am. Chem. Soc.* **77**, 6637 (1955).

[92] R. M. Acheson, *J. Chem. Soc.* p. 4731 (1956).

VI. Physical Properties

A. Ionization Properties

Quinoxalines, because of the 1:4 arrangement of their ring nitrogen atoms, are only weakly basic. The effect of substituents on basic strength is illustrated in Table II; thus α-Me, α-NH_2, α-NHMe, and

TABLE II
Ionization Constants of Quinoxalines
(in H_2O at 20°C)

Compound	Protons gained	Protons lost	Ref.
Quinoxaline	0.72[a]	—	*b*
2-Methylquinoxaline	0.95[a]	—	*b*
Quinoxalin-2-one	−1.37[c]	9.08	*d*
1-Methylquinoxalin-2-one	−1.15[e]	—	*f*
2-Methoxyquinoxaline	0.28[e]	—	*f*
3-Methylquinoxalin-2-one	0.48[e]	9.88[g]	*f*
1,3-Dimethylquinoxalin-2-one	0.51[e]	—	*f*
2-Methoxy-3-methylquinoxaline	1.38[e]	—	*f*
5-Hydroxyquinoxaline	0.9	8.65	*h*
5-Hydroxyquinoxaline 1-methiodide	—	5.74	*h*
6-Hydroxyquinoxaline	1.40	7.92	*h*
Quinoxaline-2,3-dione	—	9.52	*d*
Quinoxaline-2-thione	−1.11[e]	7.72[i]	*f*
1-Methylquinoxaline-2-thione	−0.89[e]	—	*j*
2-Methylthioquinoxaline	0.26[e]	—	*f*
2-Aminoquinoxaline	3.96	—	*k*
2-Methylaminoquinoxaline	4.10[g]	—	*f*
2-Dimethylaminoquinoxaline	3.72[l]	—	*f*
1-Methylquinoxalin-2-oneimine	8.70[g]	—	*j*
5-Aminoquinoxaline	2.62	—	*k*
6-Aminoquinoxaline	2.95	—	*k*
2,3-Diaminoquinoxaline	4.70	—	*k*

[a] Reported as thermodynamic constants.

[b] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.* p. 3832 (1954).

[c] Determined spectroscopically.

[d] A. Albert and J. N. Phillips, *J. Chem. Soc.* p. 1294 (1956).

[e] Determined spectroscopically at room temperature which varied from 15–25°C.

[f] Reference in footnote 67.

[g] At 25°C.

[h] Reference in footnote 94.

[i] In 50% ethanol at 25°C.

[j] G. W. H. Cheeseman, unpublished work.

[k] A. Albert, R. Goldacre, and J. N. Phillips, *J. Chem. Soc.* p. 2240 (1948).

[l] In 10% ethanol at 25°C.

α-NMe_2 groups are base-strengthening and α-OMe and α-SMe groups are base-weakening. 5- and 6-Amino- and hydroxy-quinoxalines are stronger bases than quinoxaline itself and 5-aminoquinoxaline is exceptional in undergoing protonation at the amino group rather than at a ring nitrogen atom.[93] This is indicated by the closely similar ultraviolet spectrum of the cation of 5-aminoquinoxaline and that of the quinoxaline neutral molecule (cf. the closely similar ultraviolet spectrum of the anilinium ion and benzene). The basic center in 5-hydroxyquinoxaline is nitrogen-1. Thus reaction of 5-hydroxyquinoxaline with methyl iodide gives a methiodide which must be the 1-methiodide, because of its ability to form a strongly bound nickel complex.[94]

The acidic strength of various quinoxaline derivatives is also listed in Table II. α-Methyl groups have an acid-weakening effect and quinoxalin-2-one (2-hydroxyquinoxaline) is, as expected, a weaker acid than quinoxaline-2-thione (2-mercaptoquinoxaline). The marked enhancement of the acidic strength of 5-hydroxyquinoxaline 1-methiodide compared to 5-hydroxyquinoxaline itself, is due to the electron-attracting property of the positively charged nitrogen.[94]

B. Ultraviolet Absorption Spectra

The ultraviolet absorption spectrum of quinoxaline in cyclohexane shows bands with vibrational fine structure at 340 (log ϵ 2.84), 312 (log ϵ 3.81), and 232 mμ (log ϵ 4.51) and which are attributable to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions.[95] In ethanol the vibrational fine structure disappears and the less intense $n \rightarrow \pi^*$ band appears as a shoulder on the long-wave $\pi \rightarrow \pi^*$ band,[96] but in methanol[97] and water[98] the less intense $n \rightarrow \pi^*$ band is obscured by the long-wave $\pi \rightarrow \pi^*$ band. In the latter solvent, the absorption maxima are at 316 (log ϵ 3.79) and 234 mμ (log ϵ 4.47). The weak $n \rightarrow \pi^*$ bands in the ultraviolet spectra of 6-chloro- and 6-bromo-quinoxaline[99] and certain 2-substituted quinoxalines also show similar shifts to shorter wavelengths on change from a nonpolar to a polar solvent, whereas the $\pi \rightarrow \pi^*$ bands are not greatly affected by change of solvent. Substitution in the quinoxaline nucleus at position 2 produces bathochromic shifts in the $\pi \rightarrow \pi^*$ bands. This increases in the order $Me < Cl < OMe < SMe < NMe_2$.[67] These substituents produce similar bathochromic effects on the 260-mμ band of the benzene spectrum and the 300-mμ band of the pteridine spectrum.[100] In a further study of substituent effects on the ultraviolet absorption properties of quinoxalines, the spectra of thirteen methyl-, alkoxy-, and halogeno-quinoxalines have been measured in nonpolar and polar solvents.[101]

[93] A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.* p. 4191 (1956).
[94] A. Albert and A. Hampton, *J. Chem. Soc.* p. 505 (1954).
[95] S. F. Mason, *Chem. Soc. (London) Spec. Publ. No. 3,* p. 139 (1955).
[96] G. M. Badger and J. S. Walker, *J. Chem. Soc.* p. 122 (1956).
[97] F. Bohlmann, *Chem. Ber.* **84,** 860 (1951).
[98] A. Albert, D. J. Brown, and G. W. H. Cheeseman, *J. Chem. Soc.* p. 474 (1951).
[99] R. C. Hirt, T. F. King, and J. C. Cavagnol, *J. Chem. Phys.* **25,** 574 (1956).

C. Infrared Absorption Spectra

Low-frequency bands for quinoxaline and seventeen of its derivatives have been reported,[101a] and a systematic study of the infrared absorption of monosubstituted quinoxalines has been carried out.[102] In this study the infrared spectrum of quinoxaline, nine of its 2-substituted, five of its 5-substituted, and eight of its 6-substituted derivatives were measured in chloroform solution. Eight ring-stretching bands are found in the region 1620–1350 cm^{-1} at frequencies close to those observed for substituted quinolines. The positions of these bands are not very sensitive to the orientation or nature of the substituents but the intensity of the bands is much more variable. Thus the intensity of the band near 1600 cm^{-1}, observed for 2-, 5-, and 6-monosubstituted quinoxalines, rises as the substituents change from electron acceptors to electron donors. Band sequences in the region 1300–800 cm^{-1} have been assigned to in-plane β-CH bending modes (at ca. 1300–1050 cm^{-1}), ring breathing modes (near to 1000 cm^{-1}), and out-of-plane γ-CH bending modes (in the region below 1000 cm^{-1}). Previous work on substituted naphthalenes[103] and quinolines[104] showed that the two rings may be considered independently for the β-CH and γ-CH modes, and tentative band assignments for monosubstituted quinoxalines are based on comparisons with the earlier work. Bands assigned to in-phase out-of-plane CH bending modes are listed in Table III.

[100] S. F. Mason, *J. Chem. Soc.* p. 2336 (1955).
[101] H. H. Perkampus, *Z. Naturforsch.* **17a,** 614 (1962).
[101a] H. H. Perkampus and A. Roders, *Z. Naturforsch.* **15b,** 1 (1960).
[102] G. W. H. Cheeseman, A. R. Katritzky, and B. J. Ridgewell, *J. Chem. Soc.,* to be published.
[103] J. G. Hawkins, E. R. Ward, and D. H. Whiffen, *Spectrochim. Acta* **10,** 105 (1957).
[104] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* p. 2942 (1960).

TABLE III
BANDS ASSIGNED TO IN-PHASE OUT-OF-PLANE CH BENDING MODES IN QUINOXALINES

Position of hydrogen atoms	Parent (cm^{-1})	2-Substituted (cm^{-1})	5-Substituted (cm^{-1})	6-Substituted (cm^{-1})
Two hydrogens at 2 and 3	866	—	867–858	868–861
Three hydrogens at 5, 7, and 8	—	—	—	832–812
Three hydrogens at 6, 7, and 8	—	—	835–825	—
Four hydrogens at 5, 6, 7, and 8	757	765–755	—	—

The infrared spectra of twelve di-, tri-, and tetra-substituted quinoxalines have also been reported.[105]

ADDENDUM

Unequivocal syntheses of *cis-* and *trans-dl*-decahydroquinoxalines have been achieved by lithium aluminum hydride reduction of the corresponding *cis-* and *trans*-decahydroquinoxalin-2-ones. The latter compounds were prepared by condensation of chloroacetic acid and *cis-* and *trans*-1,2-diaminocyclohexane, respectively. The resolution of *trans-dl*-decahydroquinoxaline was effected by use of first dibenzoyl-*d*-tartaric acid and then of dibenzoyl-*l*-tartaric acid.[106]
(*Cf.* p. 215.)

[105] H. N. Rydon and K. Undheim, *J. Chem. Soc.* p. 4685 (1962).
[106] E. Brill and H. P. Schultz, *J. Org. Chem.* **28**, 1135 (1963).

The Reactions of Diazomethane with Heterocyclic Compounds

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Diazomethane, which was first prepared in 1894 by von Pechmann,[1] undergoes numerous reactions.[2,3] In the heterocyclic series, its reactions can be divided into the following types:

(1) Methylations—lactams, thiolactams, amino compounds, and enols.

(2) Other reactions.

I. Methylation with Diazomethane

A. Reaction Mechanisms

One of the most important applications of diazomethane depends on its ability to replace a mobile hydrogen atom by a methyl group. In comparison with other methylation agents, diazomethane occupies a rather special place: this is, in part, because only rather strongly acidic protons are replaced. Because of the simple method of working up the reaction mixture, the reaction is especially well applicable for sensitive compounds and for small amounts. If tautomeric or potentially tautomeric compounds are treated with diazomethane, two

[1] H. von Pechmann, *Ber. deut. chem. Ges.* **27**, 1888 (1894).
[2] B. Eistert, *in* "Neuere Methoden der präparativen organischen Chemie," pp. 359–412. Verlag Chemie, Berlin, 1944.
[3] R. Huisgen, *Angew. Chem.* **67**, 439 (1955).

reactive centers are available for reaction; the methylated products are frequently different from those which are obtained by other methods, e.g., methylation with methyl iodide and alkali. This is a further fact which differentiates methylation by diazomethane.

$$Z—H + CH_2N_2 \rightarrow Z—CH_3 + N_2 \quad (1)$$

The general equation (1) for the methylation of a sufficiently acidic compound Z—H with diazomethane shows that the reaction formally takes place in two steps. Diazomethane does not itself contain a methyl group, thus the first step, Eq. (2), must involve the loss of a proton from Z—H and that it is taken up by diazomethane to give the corresponding cation $CH_3—N_2^+$ which is the actual methylating agent:

$$Z—H + CH_2N_2 \rightarrow Z^- + CH_3—N_2^+ \quad (2)$$

For the transfer of the methyl group from $CH_3—N_2^+$ to the anion Z^- there are two possibilities [Eqs. (3) and (4)]:

$$\begin{aligned} CH_3—N_2^+ &\rightarrow CH_3^+ + N_2 \\ CH_3^+ + Z^- &\rightarrow CH_3—Z \end{aligned} \quad (3)$$

$$Z^- + CH_3—N_2^+ \rightarrow Z—CH_3 + N_2 \quad (4)$$

In Eq. (3), the unstable methyl diazonium ion decomposes by S_N1 reaction into nitrogen and a methyl cation which combines with the anion Z^- to give $CH_3—Z$. In Eq. (4) an S_N2 reaction occurs. The loss of the nitrogen from $CH_3—N_2^+$ here takes place only with the participation of the anion as nucleophile.

What evidence is there for the individual reaction steps? The acid-base reaction (Eq. 2) has the characteristics of a Broensted equilibrium, as has been shown in the case of diazomethane–benzoic acid (in toluene).[4] Further evidence for this is provided by the reactions of diazoacetic ester[5] and diazo ketones.[6,7] The occurrence of free, mobile diazonium cations is also supported by the fact that solutions of diazomethane in methanol show greater conductivity than solutions of pure solvent.[8]

The basic properties of diazomethane have been utilized in the

[4] R. Huisgen and H. Stangl, private communication (1960).
[5] J. D. Roberts, C. M. Regan, and I. Allen, *J. Am. Chem. Soc.* **74**, 3679 (1952).
[6] J. F. Lane and R. L. Feller, *J. Am. Chem. Soc.* **73**, 4320 (1951).
[7] C. E. McCauley and C. V. King, *J. Am. Chem. Soc.* **74**, 6221 (1952).
[8] H. Bredereck, R. Sieber, and L. Kamphenkel, *Chem. Ber.* **89**, 1169 (1956).

liberation of heterocyclic bases from their salts, e.g., the preparation of 1,3,5-triazine,[9] and the neutralization of the hydrochlorides of several oxazol-5-ones.[10]

Evidence that the actual methylation of the anion can be divided into S_N1, Eq. (3), and S_N2 types, Eq. (4), is provided by a whole series of investigations.[11–19] The terms S_N1 and S_N2 must be taken to mean reactions with, respectively less or greater nucleophilic participation of the anion in the transition state. The importance of "oriented ion pairs" in the solvents of low polarity frequently used in reactions involving diazomethane, e.g., the ions formed by a diazoalkane and benzoic acid in ether, should be emphasized. The expression "oriented ion pair" means that, because of insufficient solvation, the ions are not individually solvated but exist as ion pairs within a solvent cage.[11,20,21] The orientation within the ion pair is defined electrostatically, and this orientation fixes the path for the product-determining step. Several indications (cf. footnotes 22–24) in the literature indicate the occurrence of carbonium ions and oriented ion pairs in Broensted-type equilibria of the type of Eq. (2).

If these considerations and investigations are taken into account, the reaction scheme, Eqs. (5), (6), and (7), can be deduced for the methylation of tautomeric and potentially tautomeric compounds by diazomethane (itself a special case of a reaction of ambifunctional compounds with electrophilic reagents). A vital step in this scheme

[9] C. Grundmann and E. Kober, *J. Org. Chem.* **21**, 641 (1956).
[10] "The Chemistry of Penicillin" (H. T. Clarke, J. R. Johnson, and R. Robinson, eds.), pp. 731, 911. Princeton Univ. Press, Princeton, New Jersey, 1949.
[11] R. Huisgen and C. Rüchardt, *Ann.* **601**, 1, 21 (1957).
[12] D. Y. Curtin and S. M. Gerber, *J. Am. Chem. Soc.* **74**, 4052 (1952).
[13] J. D. Roberts, W. H. Watanabe, and R. E. McMahon, *J. Am. Chem. Soc.* **73**, 760, 2521 (1951).
[14] L. P. Hammett, "Physical Organic Chemistry," p. 288. McGraw-Hill, New York, 1940.
[15] G. Bredig and P. Ripley, *Ber. deut. chem. Ges.* **40**, 4015 (1907).
[16] J. N. Broensted and H. C. Duus, *Z. physik. Chem.* **117**, 299 (1925).
[17] F. C. Whitmore and D. P. Langlois, *J. Am. Chem. Soc.* **54**, 3441 (1932).
[18] A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.* **79**, 2888 (1957).
[19] A. Streitwieser, Jr., *J. Org. Chem.* **22**, 861 (1957).
[20] R. Huisgen and H. Reimlinger, *Ann.* **599**, 161, 183 (1956).
[21] E. D. Hughes, C. K. Ingold, S. Patai, and Y. Pocker, *J. Chem. Soc.* p. 1206 (1957).
[22] D. E. Applequist and D. E. McGreer, *J. Am. Chem. Soc.* **82**, 1956 (1960).
[23] A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.* **79**, 2893 (1957).
[24] E. Pfeil and O. Weissel, *Chem. Ber.* **91**, 1170 (1958).

$$\left.\begin{matrix} Y{=}R{-}X{-}H \\ H{-}Y{-}R{=}X \end{matrix}\right\} + CH_2N_2 \rightleftarrows \left[\begin{matrix} Y{=}R{-}X^- \\ \updownarrow \\ {}^-Y{-}R{=}X \end{matrix}\right] + CH_3{-}N_2^+ \quad (5)$$

$$CH_3{-}N_2^+ \rightarrow CH_3^+ + N_2 \quad (6a)$$

$$CH_3^+ + A^- \rightarrow CH_3{-}X{-}R{=}Y \quad (6b)$$

$$A^- + CH_3{-}N_2^+ \rightarrow [A^{\delta-} \ldots CH_3 \ldots N_2^{\delta+}] \rightarrow CH_3{-}Y{-}R{=}X + N_2 \quad (7)$$

(A^- = mesomeric anion)

is the formation of a mesomeric anion in the preliminary equilibrium (which need not necessarily come to completion) [Eq. (5)]. Hence it is not possible to deduce the structure of the product from the structure of the starting material. Further, it can be seen, Eq. (5), that diazomethane acting as a base can catalyze the tautomeric rearrangement of the starting material.

The reasons why the two final stages Eqs. (6b) and (7), lead to different products must now be stated: they lie in the different causes of S_N1 and S_N2 reactions.

In an S_N1 reaction the rate-determining step involves the production of ions, which are stable only when solvated. The cations (e.g., carbonium ions) are usually highly energetic, and therefore only weakly selective. Hence, all the factors which determine the structure of the solvent sheath, especially in the immediate neighborhood of the cation, will also influence the product-formation step. The major factor controlling the interaction between ions in solution[24a] is electrostatic attraction. This is important at relatively large distances,[25,26] certainly at larger distances than are necessary for the formation of a covalent bond.[27] The electrostatic attraction is a function of the electron density in the cation and the anion: it is the stronger the greater the electron density in the anion and the smaller in the cation. The importance of the ion pair concept can now be realized. The assumption has to be made that the formation of the new bond, in the S_N1 reaction, Eq. (6b), is predominantly although not completely determined by the electrostatic attraction between the methyl cation and the atom of greatest electron density in the mesomeric

[24a] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," pp. 123–159. Wiley, New York, 1961.
[25] W. J. Moore, "Physical Chemistry," pp. 296, 297. Prentice Hall, New York, 1956.
[26] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," pp. 33–35. Cornell Univ. Press, Ithaca, New York, 1953.
[27] M. Bersohn, *J. Am. Chem. Soc.* **83**, 2137 (1961).

cation anion. (In the equations, X is thus the atom with the greatest electron density and Y that with the greater nucleophilicity.)

In contrast to S_N1 reactions, the S_N2 type represent a one-step process. The rate-determining stage, and hence the formation of the new bond, depends on the nucleophilicity of the anion (the nucleophilicity[28] is essentially a function of the polarizability[28a]). In the S_N2 reaction under discussion, Eq. (7), the nitrogen in $CH_3{-}N_2^+$ is replaced by the atom of the mesomeric anion which possesses the greatest nucleophilicity.

Much evidence can be found for this interpretation of the product-determining stage among competitive S_N1 and S_N2 reactions, in general; for example, the important investigations of Kornblum *et al.*[29] on the reactions of metal nitrites with alkyl halides. Other evidence is provided by the behavior of acid amides toward alkylating agents[30,31] and the discovery[32] that the action of alkyl halides on mixtures of ethyl alcohol and ethylamine give a larger proportion of ether the greater the S_N1 character of the reaction.

The classical theory of methylation with diazomethane was developed by Arndt[2,3,33,34] from a different basis. It depends on the postulate (which can be traced back to von Pechmann[35–37]) of "direct methylation": mobile hydrogen in an acid compound is directly replaced by the methyl group, i.e., the methyl group appears in the place which the hydrogen previously occupied. For the reaction of tautomeric substances with diazomethane, the following equation is applicable:

$$Y{-}CH_3 \overset{CH_2N_2}{\underset{v_4}{\leftarrow}} Y{-}H \overset{v_1}{\underset{v_2}{\rightleftarrows}} X{-}H \overset{CH_2N_2}{\underset{v_3}{\rightarrow}} X{-}CH_3 \quad (8)$$

[28] C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.* **75**, 141 (1953); J. O. Edwards, *ibid.* **76**, 1540 (1954).
[28a] J. O. Edwards, *J. Am. Chem. Soc.* **78**, 2770 (1956).
[29] N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.* **77**, 6269 (1955).
[30] R. Gompper and O. Christmann, *Chem. Ber.* **92**, 1935 (1959).
[31] H. Bredereck, R. Gompper, and G. Theilig, *Chem. Ber.* **87**, 537 (1954).
[32] W. Hägele, Diplomarbeit Techn. Hochschule Stuttgart, 1962.
[33] F. Arndt, *in* "Organic Analysis" (J. Mitchell, Jr., J. M. Kolthoff, E. S. Proskauer, and A. Weissberger, eds.), Vol. I, pp. 197–241. Interscience, New York, 1953; *Angew. Chem.* **61**, 397 (1949).
[34] F. Arndt, *Abhandl. braunschweig. wiss. Ges.* **8**, 1–15 (1956).
[35] H. von Pechmann, *Ber. deut. chem. Ges.* **28**, 856 (1895).
[36] H. von Pechmann, *Ber. deut. chem. Ges.* **28**, 1624 (1895).
[37] H. von Pechmann and O. Degner, *Ber. deut. chem. Ges.* **30**, 1624 (1897).

Here Y—H is the tautomeric form with the smaller, and X—H that with the larger, dynamic acidity.

The velocities (v_3, v_4) of the two methylation reactions depend both on the equilibrium concentration of Y—H and X—H and, most importantly, on their dynamic acidity. Form X—H reacts more quickly; thus X—H is formed from Y—H by tautomeric change. If both the forms have a sufficient dynamic acidity for reaction, XCH_3 and YCH_3 are formed simultaneously, but the proportion of XCH_3 in the product is larger than that of X—H in the initial equilibrium. If only X—H is acid enough to react, then the whole of the material is converted to XCH_3 via the equilibrium. Any OH form (e.g., an enol) has a considerably greater dynamic acidity than the corresponding CH or (with less difference) NH form.

The process of the "direct methylation" is interpreted in the following way [Eq. (9)]: initially the hydrogen-bonded complex **1** is

$$\mathrm{X{-}H + CH_2N_2 \longrightarrow X{-}H\cdots CH_2N_2 \longrightarrow}$$

(1)

$$\mathrm{N_2 + X{-}H{-}CH_2 \longrightarrow X{-}CH_3} \qquad (9)$$

(2) (3)

formed. The more the hydrogen-bonding proton belongs to the carbon atom of diazomethane, the less stable the diazo group and the greater the probability of eliminating nitrogen. Structure **2** is continually transformed into structure **3**.

The foregoing investigations which demonstrate the equilibrium character of the primary step in methylation with diazomethane necessitate the additional assumption for Eq. (9) that the complex **1** shows the properties of an oriented ion pair (there is evidence[38-41] which can be thus interpreted) and the formation of **1** is reversible. It should be noted that in no stage of the process (including complex **1**) is a mesomeric anion formed. A "direct methylation" is only possible when the compound retains a "fixed" structure throughout the reaction.

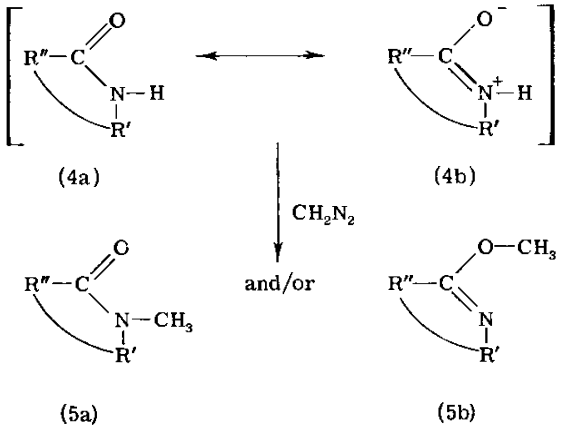
[38] D. B. Denney, *J. Am. Chem. Soc.* **77**, 1706 (1950).
[39] J. S. Ard and T. D. Fontaine, *Anal. Chem.* **23**, 133 (1951).
[40] G. M. Barrow and E. A. Yerger, *J. Am. Chem. Soc.* **76**, 5211 (1954). E. A. Yerger and G. M. Barrow, *J. Am. Chem. Soc.* **77**, 4474 (1955).
[41] M. M. Davis and M. Paabo, *J. Am. Chem. Soc.* **82**, 5081 (1960).

The two theories have been directly compared.[42]

B. Methylation of Lactams[43]

In respect to the general reaction scheme [Eqs. (5) to (7); X = O, Y = NR′, R = CR″, and Y and R are part of a ring], two questions can be asked:

1. How acidic must the lactam be in order to react with diazomethane?
2. Are lactams methylated on nitrogen or on oxygen [Eq. (10)], and what structural criteria determine *N*- or *O*-methylation (5a,b)?



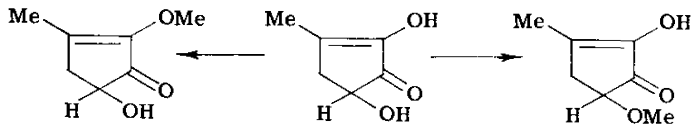
(10)

The first question can be answered relatively simply (although not completely exactly) from the available factual material. If the p*K* value of the lactam is taken as a criterion, the border of reactivity lies at about p*K* 12. Valerolactam and caprolactam react just noticeably with diazomethane (yields 14 and 7%).[44] However, it should be noticed that catalysts are frequently necessary in order to initiate the reaction (methanol, water, aluminum isopropylate,[45] fluoboric acid[44]). For example, phthalimide does not react at all with diazomethane in ether, but a smooth reaction occurs if some methanol is added.

[42] F. Arndt, B. Eistert, R. Gompper, and W. Walter, *Chem. Ber.* **94**, 2125 (1961).
[43] R. Gompper, *Chem. Ber.* **93**, 187, 198 (1960).
[44] J. W. Ralls, *J. Org. Chem.* **26**, 66 (1961).
[45] H. Zinner, O. Schmitt, W. Schritt, and G. Rembarz, *Chem. Ber.* **90**, 2852 (1957).

To answer the second question, information as to the degree of nucleophilic participation of the amide anion in the fission of the C—N bond in $CH_3—N_2^+$ is required. The essential point is whether the added amide favors the S_N2 or the S_N1 reaction. The reaction velocity is constant for Eq. (6), but in the case of Eq. (7) it depends on the nucleophilicity of the anion—hence, the nucleophilic strength determines the reaction type. [For the reaction of a weakly nucleophilic anion with $CH_3—N_2^+$, the irreversible decomposition of the unstable $CH_3—N_2^+$, Eq. (6a), is quicker than the substitution according to Eq. (7).] It might be thought that the acidity of the lactams would give such information as to the nucleophilicity. However, on this view, it is surprising that phthalimide yields *N*-methylphthalimide but 2-pyridone is converted to 2-methoxypyridine: phthalimide is considerably more acid than 2-pyridone; thus, its anion is less strongly basic than that of 2-pyridone. It is certainly not possible to equate basicity and nucleophilicity, although in a series of similar compounds the two quantities usually follow each other. If phthalimide and 2-pyridone could be considered as the same type of compounds, then it should follow that the anion of 2-pyridone would be more nucleophilic than that of phthalimide, and thus 2-pyridone should undergo an S_N2 reaction whereas in the case of phthalimide the S_N1 reaction should be favored. However, according to the methylation results, exactly the opposite must hold.

Thus, the acidity of a lactam is evidently not a reliable quantity for predicting the course of the methylation. The acidity gives information only as to the reaction velocity. In this connection the reaction course of isomethylreductone (**6**) is illuminating.[46] With diazomethane in ether containing 1 mole of water, the enolmethyl ether (**7**) is formed. However, if water is present only in traces, then the alcoholic hydroxyl group is selectively attacked to give **8**.

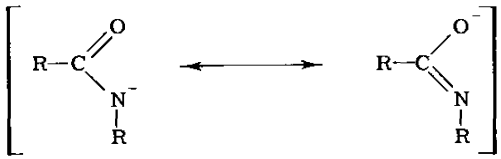


(7) (6) (8)

In amide anions, the nitrogen atom is generally more nucleophilic than the oxygen. The nitrogen atom will possess an especially high

[46] G. Hesse, F. Exner, and H. Hertel, *Ann.* **609**, 60 (1957).

nucleophilic potential in those amide anions in which the canonical form (**9a**) is the most important structure in the ground state (**9**),



(9a) (9b)

because of lack of or weak mesomerism. By contrast, for amide anions in which maximum mesomeric stabilization occurs (i.e., the participation of the canonical form **9b** is approximately 50%), the nucleophilicity of the nitrogen is weaker because the electron density on the oxygen is correspondingly greater. The degree of nucleophilic participation in the transition state depends on the position of a definite anion between these two extremes. The connection between "hindered" mesomerism and increased nucleophilicity is illustrated by the larger dynamic basicity of the anion of dinitromethane than that of nitromethane.[47] The protonation of carbanions stabilized by SO_2 groups should also be mentioned.[48]

A criterion for the position of the extent of the mesomerism of type **9** is given by the bond order of the CO bond, a first approximation to which can be obtained from the infrared spectrum (ν C=O). Unfortunately, relatively little is known of the infrared spectra of amide anions. However, it can be assumed that the mesomeric relationships in the anions **9** can also be deduced from the infrared spectra of the free amides (**4**), although, of course, the absolute participation of the canonical forms **a** and **b** in structures **4** and **9** is different. If Table I is considered from this point of view, the intimate relationship between the position of the amide band 1 (ν C=O) and the orientation (O or N) of methylation of lactams by diazomethane is unmistakeable. Thus the behavior of a lactam toward diazomethane can be deduced from the acidity (velocity of reaction) and the C=O stretching frequency (orientation of methylation). Three major regions can be differentiated: (1) 1620–1680 cm^{-1}, *O*-methylation; (2) 1680–1720 cm^{-1}, *O*- and *N*-methylation, with kinetic dependence; and (3) 1730–1800 cm^{-1}, *N*-methylation. The factual material in Table I is

[47] R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.* **75**, 2439 (1953).
[48] H. E. Zimmermann and B. S. Thyagarajan, *J. Am. Chem. Soc.* **82**, 2505 (1960).

TABLE I

METHYLATION OF LACTAMS WITH DIAZOMETHANE AND IR SPECTRA OF LACTAMS[a]

Lactam	Methylation, O-	Methylation, *N*-	O:N[b]	Total yield (%)	Process[c]	νC=O (cm^{-1})
3-Hydroxy-5-phenylisothiazole	Trace	+[49]	—	89	B	1575[49;d]
						1565
2-Cyanoquinol-4-one	+[50]		—	55	B	1595[50]
1-Phenyl-3-oxodihydropyrazolo-[3,4-*d*]pyrimidine	+[50a]		—	82	B	1611
4-Hydroxypyrid-2-one-6-carboxylic acid		+[51]	—	92	A	1612
Quinol-4-one	+[52]		—	81	A,C	1628[53]
						[1648[54]]
Pyrid-4-one	+[55]	+[55]	1:1	—	A	1638[54]
6-Phenylpyrid-2-one	+[43]		—	37	A	1642
1,3-Dimethylpteridine-2,4,6-trione	+[56]		—	38	B	1645[57;e]
Quinol-2-one	+[55]		—	—	A	1650[53,54,58]
Pyrid-2-one	+[59]		—	—	A	1650[54]
1,3,6-Trimethylpteridine-2,4,7-trione	+[60]		—	85	B	1655[57;e]
2-Phenyl-3-oxodihydropyrazolo-[3,4-*d*]pyrimidine	+[50a]	+[50a]	1:4	47	B	1655
Phthalazone		+[43]	—	75	C	1657
Phthalic acid hydrazide	+[61]		—	75–90	A	1658
4-Phenylthiazol-2-one		+[43]	—	75	B	1659
Thiazol-2-one	+[62]	+[62]	4:3	61	A	1660[62]
4-Methylthiazol-2-one	+[63]		—	—	B	1660
4-Methyl-6-phenylpyrimidin-2-one	+[43]		—	45	B	1660
4,6-Diphenyl-1,3,5-triazin-2-one	+[43]	+[43]	5:1	89	C	1660
Caprolactam	+[44]		—	7	A	1660[64]
1,3-Dimethylpteridine-2,4,7-trione	+[60]		—	38	B	1660[57;e]
N-Phenyl-*N*,*N*′-succinylhydrazine	Trace	+[61]	—	90	A	1662
Valerolactam	+[44]		—	14	B	1667[64]
2-Methyl-6-phenylpyrimidin-4-one		+[43]	—	75	C	1670
5-Ethoxycarbonylpyrimidin-4-one	+[65]	+[65]	4:1	95	B	1671
Maleic acid hydrazide	+[61]		—	82	A	1675
						1657
1,3,4-Benzotriazin-2-one-4-oxide	+[66]	+[66]	3:2	90	F	1676
			2:3	90	E	
2,6-Dimethylpyrimidin-4-one	+[43]	+[43]	5:4	67	C	1679
						1661

TABLE I (*Continued*)

Lactam	Methylation, *O*-	Methylation, *N*-	O:N[b]	Total yield (%)	Process[c]	νC=O (cm^{-1})
Guanosine		+[67]	—	62	B	1687[f]
						1657
						1638
4,6-Dimethoxy-1,3,5-triazin-2-one	+[68]		—	—	A	1686
Quinoxalin-2-one	+[69]	+[69]	1:2	76	D	1690
						1679
2-Methoxy-quinoxalin-3-one	+[69]	+[69]	2:3	97	B	1690
Pteridin-7-one	+[70]	+[70]	1:99	32	D	1693[71]
Naphthalimide		+[43]	—	83	B	1696
						1678
Diphenimide		+[72]	—	73	A	1696
						1675
5,5-Diphenyl-1,2,4-oxadiazolin-3-one		+[73]	—	39	B	1701[73]
Pteridine-2,4-dione		+[74]	—	69	B	1703[g]
						1684
Uric acid	+[75]	+[75]	*h*	—	A	1704
						1689
						1673
Quinazolin-4-one	+[76]	+[76]	1:2	55	B	1704
		+[43]		91	B	1671
Quinoxaline-2,3-dione	+[69]	+[69]	1:1	95	D	1706
						1678
Pteridin-4-one	+[70]	+[70]	1:3	77	B	1710[71]
						1697
Pyrimidin-4-one	+[77]	+[77]	1:5	51	A	1716[54]
						1684
3,6,8-Trimethylpteridine-2,4,7-trione	+[78]		—	66	B	1716[57;e,i]
						1711
Benzoylene urea (quinazoline-2,4-dione)		+[61]	—	90	B	1724
						1703
						1674
Glutarimide		+[72]	—	—	A	1725
						1707
						1669
Saccharin[78a–81]		+[33,81]	—	—	A[i]	1725
	+	+	1:9	—	E	
	+	+	1:3	—	F	
Pyrimidin-2-one	+[77]	+[77]	1:3	69	A	1733[54]
						1674
Thiazolidine-2,4-dione		+[62]	—	—	A[82]	1740
						1684

TABLE I (*Continued*)

Lactam	Methylation, *O*-	Methylation, *N*-	O:N[b]	Total yield (%)	Process[c]	νC=O (cm^{-1})
4,5-Diphenyloxazolin-2-one		+[83]	—	94	B	1750
Barbituric acid		+[84]	—	53	A	1754
						1746
						1723
						1711
						1694
5-Phenyl-1,3,4-oxadiazolin-2-one		+[43]	—	85	B	1764
						1747
Uracil, thymine		+[85]	—	98	A,B	1768[86]
						1737
						1716
						1673
						1653
1-Phenylurazole	+[87]	+[87]	*h*	—	A	1768
						1701
1,9-Diacetylspirodihydantoin		+[88]	—	100	A	1768[k]
						1736
						1709
Benzoxazolin-2-one		+[89]	—	92	A	1769
						1740
3-Phenyl-1,2,4-oxadiazolin-5-one		+[43]	—	75	A	1769
Phthalimide		+[78a–80]	—	—	C	1774
						1749
						1724
4-Phenylurazole		+[90]	—	87	A	1775
						1754
						1687
Succinimide		+[61]	—	88	A	1776
						1748
						1695
Cyanuric acid		+[91]	—	100	A	1777
						1753
						1723
						1707
Urazole	+[90]	+[90]	*h*	—	A	1794
						1683

[a] Spectra obtained as KBr disks.

[b] Ratio of *O*- to *N*-methylation.

[c] Experimental procedures: A: The substance is dissolved or suspended in ether and treated with ethereal diazomethane. B: The substance is dissolved in methanol (or ethanol, acetone, chloroform) and reacted with ethereal diazomethane. C: A solution or suspension of the substance in ether is mixed with ethereal diazomethane, and methanol is then added until noticeable reaction occurs. D: The same as in case B but at temperatures at or below 0°C. E: Addition of the substance as such, or as a saturated solution, to concentrated ethereal diazomethane. F: Slow addition of ethereal diazomethane to a dilute solution or suspension of the substance in ether.

[d] ν C=N.

[e] Only those bands are given which are assigned to the reacting amide group.

[f] IR spectrum of guanine.

[g] IR spectrum of 6,7-diethylpteridine-2,4-dione.[71]

[h] The compounds contain several amide groups and are both *N*- and *O*-methylated.

[i] IR spectrum of 1,3,6,8-tetramethylpteridine-2,4,7-trione.

[j] Benzene as solvent.

[k] IR spectrum of 5-methyl-5-ethylhydantoin.

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supplemented by the material given in Table II (without infrared spectra).

Because of the frequent mutual interference of electronic, inductive, and steric effects, and because of the influence of ring strain, the carbonyl stretching frequency is naturally not an absolute criterion for the methylation course. The heterocyclic systems in question are too diverse for this to hold. Careful inspection of Table I discloses certain deviations from the relationships mentioned. These deviations will now be discussed.

In addition to the intramolecular effects, steric factors are of considerable influence. The most usual one consists of steric hindrance to attack on the lactam nitrogen atom. Certain examples of this will be given. By comparison with uracil, it would be expected that uric acid (**10**) would be *N*-methylated in the pyrimidine ring, but that in the imidazole ring *O*-methylation should also be possible. However, the experiments of Biltz and Max[75] show that all uric acid derivatives which carry a hydrogen atom in the 9-position are converted by ethereal diazomethane into 1,3,7-trimethyl-8-methoxyxanthine (**11**). The following are examples: uric acid and its 1-methyl, 3-methyl, 7-methyl, 1,3-dimethyl, 1,7-dimethyl, 3,7-dimethyl, and 1,3,7-trimethyl derivatives. Uric acid derivatives which are substituted by alkyl groups in the 3- and 9-positions (e.g., 3,9-dimethyl-, 1,3,9-trimethyl-, and 3,7,9-trimethyl-uric acid)do not react at all with diazomethane, possibly because of insufficient acidity. Uric acids which are alkylated

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TABLE II
REACTION OF LACTAMS WITH DIAZOMETHANE[a]

Lactam	Methylation, *O*-	Methylation, *N*-	O:N ratio	Total yield (%)	Process
3-Cyano-4-ethoxycarbonyl-6-carboxypyrid-2-one	+[92]		—	—	A
3-Cyano-4-ethoxycarbonyl-6-acetylpyrid-2-one	+[92]		—	—	A
3-Keto-2,3-dihydrofuro[2,3-*b*]quinol-4-one	+[93]		—	20–38	D
2-Methylquinol-4-one	+[52]		—	—	C
6-Methyl-3-phenylquinol-4-one	+[52]		—	—	A
Quinol-2-one-4-carboxylic acid	+[55]		—	—	A
4-Hydroxyquinol-2-one	+[94]		—	20	A
5,6-Dihydroxy-2-carboxyquinol-4-one	+[95]		—	70	B
4-Methylurazole	+[90]		—	100	A
4-Methyl-1-phenylurazole	+[90]		—	60	A
3-Methyl-1-phenylpteridine-2,4,7-trione	+[78]		—	55	B
1,3-Dimethyl-6-carboxypteridine-2,4,7-trione	+[96]		—	55	B
1,3-Dimethylpteridine-2,4,6,7-tetraone	+[97]		—	32	B
4-Aminobenzoxazolone	+[98]		—	82	A
2-Methoxypyrid-4-one	+[99]	Trace	—	—	B
Tetrazolin-5-one	+[100]	+[100]		—	A
2-Phenyltriazine-4,6-dione	+[101]	+[101]	2:1	50	A
2-Diphenylmethyleneoxazolidine-4,5-dione	+[102]	+[102]	2:1	99	A
2-Aminopteridine-4,6,7-trione	+[103]	+[103]	2:1	39	B
4-Methoxypyrid-2-one	+[99]	+[99]	5:3	80	B
1-Methylquinoxaline-2,3-dione	+[69]	+[69]	5:4	96	B
1-Phenyl-4,4-diethylpyrazolidine-3,5-dione	+[61]	+[61]	1:1	100	A
6-Methyl-3-cyano-4-carboxypyrid-2-one	+[104]	+[104]		—	A
2-Methylquinoxalin-3-one	+[69]	+[69]	3:5	80	A
2-Aminoquinoxalin-3-one	+[69]	+[69]	1:3	50	B
Pyrid-2-one-3-carboxylic acid	+[55]	+[55]	1:9	—	A
Benzo-1,2,4-thiodiazin-3-one-1,1-dioxide	+[105]	+[106]	1:10	—	D
Pyrimido[5,4-*d*]pyrimidine-2,4,6,8-tetraone	+[105a]	+[105a]	—	40	C
Pyrimido[5,4-*d*]pyrimidine-2,4,8-trione	+[105a]	+[105a]	—	—	C
Cinnolin-4-one-3-carboxylic acid		+[106]	—	7	A
5-Keto-6-(4′-carboxybutyl)cyclopenteno-[*b*]pyrid-2-one		+[107]	—	58	B
3-Oxo-3,4-dihydro-1,4,5-triazanaphthalene		+[108]	—	15	B
2-Hydroxythiazolo[4,5-*b*]quinoline		+[108b]	—	76	A
2-Hydroxythiazolo[5,4-*b*]quinoline		+[108b]	—	57	A

TABLE II (*Continued*)

Lactam	Methylation, *O*-	Methylation, *N*-	O:N ratio	Total yield (%)	Process
6-Azauracil (1,2,4-triazine-3,5-dione)		+[108c]	—	91	A
6-Azathymine(5-methyl-1,2,4-triazine-3,5-dione)		+[108c]	—	87	A
Methylpyrid-2-one-3-carboxylate		+[55]	—	—	A
Thiazolidine-2,4-dione		+[62]	—	—	B
3-Hydroxy-4-phenylquinol-2-one		+[108a]	—	—	B
Pyrazoline-4,5-dicarboxylic acid imide		+[61]	—	—	A
Alloxazine		+[109]	—	98	A
1,7,8-Trimethylxanthine		+[110]	—	80	B
1,3,5-Triazine-2,4-dione		+[111]	—	—	A
4-(5,6,7)-Hydroxybenzoxazolin-2-one		+[98]	—	73–85	A
6-(7)-Aminobenzoxazolin-2-one		+[98]	—	67–75	A
4-(5,6,7)-Nitrobenzoxazolin-2-one		+[112]	—	77–86	A
5,7-Dinitrobenzoxazolin-2-one		+[113]	—	88	A
1,2-Dimethylurazole		+[90]	—	87	A
2-Methyl-1-phenylurazole		+[90]	—	100	A
1,4-Diphenylurazole		+[90]	—	—	A
4-Methyl-3-methoxyurazole		+[90]	—	—	A
1-(β-D-Glucopyranosyl)uracil		+[114]	—	—	B
2,4-Dioxo-3-azaquinolizidine		+[115]	—	—	C

[a] Footnotes *b*, *c* to Table I apply also to Table II.

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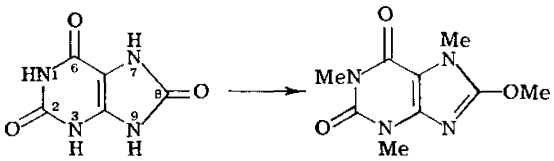
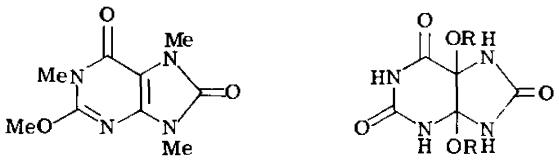
in the 9-position and unsubstituted in the 3-position give 1,7,9-trimethyl-2-methoxypurine-6,8-dione (**12a**). Diazoethane yields similar reaction products.

It is evident that methyl groups at the 3- or 9-positions suppress *N*-methylation at the 9- or 3-positions, respectively, in favor of an



(10) (11)



(12a) (12b)

O-methylation at the neighboring carbonyl groups. It is interesting that "uric acid glycols" (**12b**, R=H) and "uric acid glycol ethers" (**12b**, R = alkyl) are solely *N*-methylated; here the electronic and steric relationships are different.

The conversion of 1,3-dimethylpteridine-2,4,7-trione (**13**) to 1,3-dimethyl-7-methoxypteridine-2,4-dione (**14**)[60] and of 3,6,8-trimethyl-

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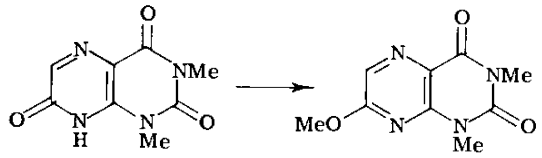
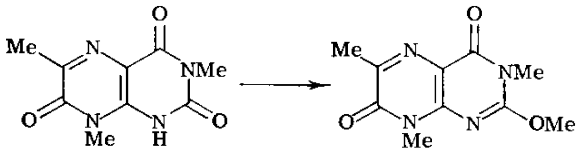
pteridine-2,4,7-trione (**15**) to 3,6,8-trimethyl-2-methoxypteridine-4,7-dione (**16**)[78] can also be interpreted as illustrations of steric hindrance. (For further examples see footnotes 96 and 97).

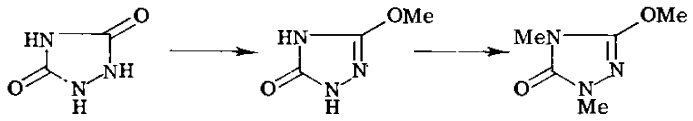


(13) (14)

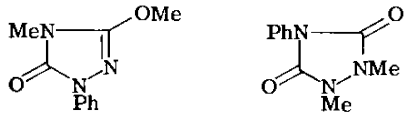


(15) (16)

Certain facts in the urazole series can also be interpreted in this way. Urazole (**17**) itself reacts with diazomethane quickly to yield 4-methyl-3-methoxy-1,2,4-triazolin-5-one (**18**), which is more slowly converted to 1,4-dimethyl-3-methoxy-1,2,4-triazolin-5-one (**19**).[90] 1-Phenylurazole gives 4-methyl-3-methoxy-1-phenyl-1,2,4-triazolin-5-one (**20**)[87]; however, 4-phenylurazole yields the 1,2-dimethyl derivative (**21**).[90] In the case of 4-methylurazole both *O*- and *N*-methylation



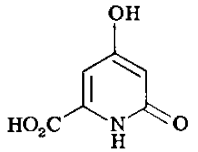
(17) (18) (19)



(20) (21)

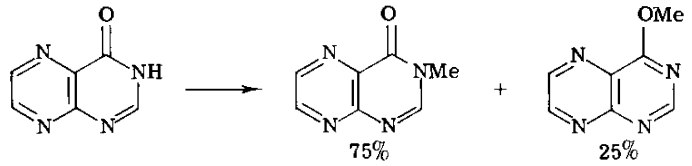
are again found,[90] but it is notable that 1,4-diphenylurazole is solely *N*-methylated.[90]

In addition to the steric effects shown especially by alkyl and aryl groups, the field effect of strongly polar groups must also be considered. For example, 4-hydroxypyrid-2-one-6-carboxylic acid (**22**)

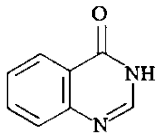


(22)

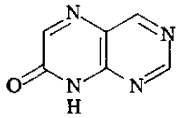
is exclusively *N*-methylated[51] in spite of its specially low carbonyl frequency. The steric effect of the carboxyl group should favor *O*-methylation; hence, the clarification must be sought on electrostatic grounds. The high electron density on the oxygen of the carboxyl (or methoxycarbonyl) group influences methylation by the methyldiazonium ion and (possibly also the methyl cation) in the sense of causing methylation on nitrogen and thus preventing it at the lactam oxygen atom. Because of the great importance of ion pairs in the reaction mechanism, such an effect of a group which could influence the orientation within the ion pair is not surprising. This interpretation is supported by the behavior of 4-methoxypyrid-2-one[99] (methylation ratio O:N = 5:3) which approximates to that of pyrid-2-one. Again pteridin-4-one (**23**) gives 25% of 4-methoxypteridine (**25**) in addition to 3-methylpyridin-4-one (**24**).[71] However, the analogous structure (**26**) on similar treatment gives only 3-methylquinazolin-4-one. Obviously, in pteridin-4-one the nitrogen atom of the pyrazine ring (N-5), which is adjacent to the carbonyl group, alters the electrostatic orientation within the ion pair, so that it favors



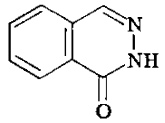
(23) (24) (25)



(26)



(27)



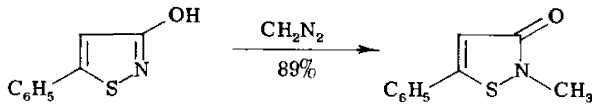
(28)

the *O*-methylation, compared to that in the quinazolin-4-one. Here, the high polarity of the C=N double bond is involved, just as it is in addition reactions (see in the following). Further evidence is that diazomethane attacks only the 8-position nitrogen of pteridin-7-one (**27**)[70]; this is favored by the neighboring nitrogen (N-1) in the pyrimidine ring. Phthalazin-1-one (**28**) is also exclusively *N*-methylated.

Urazole (**17**) and its derivatives and also maleic and phthalic acid hydrazides belong to the class of the cyclic hydrazides. The *O*-methylation observed for compounds of this type can be related[90] to the fact that one of the amide groups is present completely in the imidol form.[116-120] Although the question of the occurrence of the imidol form in the case of the semiaromatic cyclic hydrazides is not yet completely clarified (cf. footnote 121), the general reaction scheme (see p. 248) also applies to the reaction of imidols with diazomethane. The proportion of a lactam which exists in the imidol form cannot be directly related to the composition (NMe:OMe ratio) of the reaction products. This would, of course, also not be possible on the Arndt theory, although according to this theory the *O*-methylation of the cyclic hydrazides occurs because the imidol forms suffer "direct" methylation. Imidols are usually more acidic than amides[122]; in any case the "dynamic acidity" is, according to Arndt, always

[116] K. Eichenberger, R. Rometsch, and J. Drucy, *Helv. Chim. Acta* **37**, 1298 (1954).
[117] D. M. Miller and R. W. White, *Can. J. Chem.* **34**, 1510 (1956).
[118] E. A. Steck and F. C. Nachod, *J. Am. Chem. Soc.* **79**, 4408 (1957).
[119] Yu. N. Sheinker, T. V. Gortinskaya, and T. P. Sychera, *Zhur. Fiz. Khim.* **31**, 599 (1957); *Chem. Abstr.* **52**, 877 (1958).
[120] J. A. Elvidge and A. P. Redman, *J. Chem. Soc.* p. 1710 (1960).
[121] R. Gompper and P. Altreuther, *Z. anal. Chem.* **170**, 205 (1959).
[122] A. Albert and J. N. Phillips, *J. Chem. Soc.* p. 1294 (1956).

greater for an OH than for an NH form. The proportion of the methoxy derivative in the reaction mixture must, therefore, according to Arndt (as previously mentioned) always be larger than the proportion of the imidol form in the equilibrium mixture. Complete imidolization should, therefore, mean quantitative *O*-methylation. The reaction of 3-hydroxy-5-phenylisothiazole[49] (**29**) with diazomethane shows that this requirement is not always satisfied. Although compound **29** occurs, according to Goerdeler,[49] almost completely in the hydroxy form, the *N*-methyl derivative (**30**) is formed practically

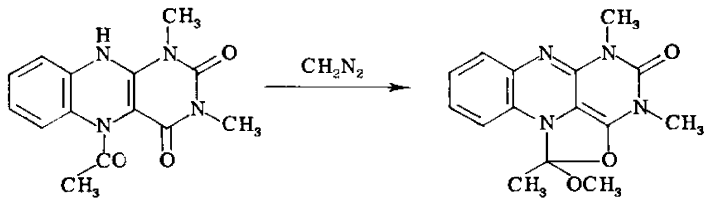


(29) (30)

ν C=N 1575 cm^{-1} ν C=O 1660 cm^{-1}

exclusively; i.e., the yield of the methoxy compound (ν C=N 1555 cm^{-1}) is much smaller than the imidol proportion in the starting material!

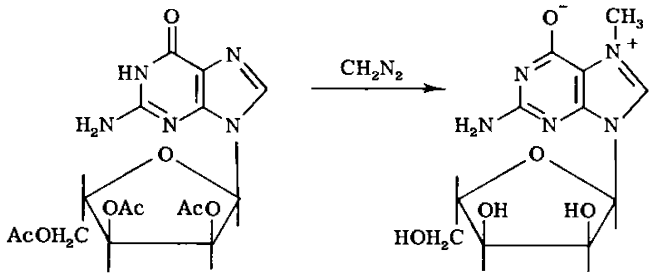
A special influence on the course of a reaction by a neighboring group is shown in the reactions of 5-acetyl-leuco(iso)alloxazines[122a] with diazomethane. The methylation occurs neither in the pyrimidine nor in the pyrazine ring, but on the hydroxyl group of a newly formed oxazoline ring. For example,



(31) (32)

The reaction of 2′,3′,5′-tri-*O*-acetylguanosine (**32a**) with diazomethane in methanol-acetone mixture may also be mentioned here.

[122a] P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta* **43**, 372 (1960).



(32a) (32b)

The 1-methoxy-compound[122b] is not formed, but rather 7-methyl guanosine (**32b**), with a betaine structure.[122c]

Finally the so-called "kinetic dependence" of methylation by diazomethane must be mentioned. (This phenomenon was first observed by Arndt in 6-methylthiacoumarindiol[123]; see later.) "Kinetic dependence" is found in various amides (or enols) which are methylated principally on nitrogen if they are introduced into excess ethereal diazomethane, but principally on oxygen if the diazomethane is gradually dropped into the ethereal amide solution (or suspension).

For example, if saccharin (**33**) is methylated in benzene suspension, then only *N*-methylsaccharin is isolated. If an ethereal saccharin solution is added to a concentrated solution of diazomethane in excess, then 10% of *O*-methylsaccharin (**34**) can be detected in addition to the *N*-methyl derivative. Finally, if the diazomethane solution is gradually added to a saturated ethereal solution of saccharin, the proportion of *O*-methylation increases to 24%.[33,81]

(33) (34)

[122b] H. Bredereck, H. Haas, and A. Martini, *Chem. Ber.* **81**, 307 (1948).
[122c] J. A. Haines, C. B. Reese, and A. R. Todd, *J. Chem. Soc.* p. 5281 (1962).
[123] F. Arndt and B. Eistert, *Ber. deut. chem. Ges.* **62**, 39 (1929).

On the basis of the general reaction scheme (see p. 248) the "kinetic dependence" is caused by the fact that the rate of the S_N2 reaction, Eq. (7), is dependent on the concentration of diazomethane but that the rate of the S_N1 reaction, Eq. (6), is not. (For unimolecular reactions, the half-life does not depend on the concentration but it does in the case of bimolecular reactions.[124] We have, assuming fast pre-equilibrium:

$$[A^-] = [CH_3N_2^+] = K[CH_2N_2]^{1/2}[HA]^{1/2}$$

$$\text{rate of } SN_1 = k_1[CH_3N_2^+] = k_1K[CH_2N_2]^{1/2}[HA]^{1/2}$$

$$\text{rate of } SN_2 = k_2[CH_3N_2^+][A^-] = k_2K[CH_2N_2][HA]$$

For high diazomethane concentrations, the S_N2 reaction, Eq. (7), and thus *N*-methylation occurs, whereas *O*-methylation is favored by lower diazomethane concentrations, Eq. (6) (for an interpretation of this effect, according to Arndt, see references **33** and **42**). The extent of this effect is limited by the constitution of the lactam in question. The fact that the addition of the sodium salt of saccharin to the reaction mixture leads to increased *N*-methylation for saccharin[43] can be taken as supporting the foregoing interpretation.

When diazomethane is slowly added to excess lactam, the anions formed can interact with unreacted lactam by means of hydrogen bonds to form ion pairs similar to those formed by acetic acid–triethylamine mixtures in nonpolar solvents.[40] The methyldiazonium ion is then involved in an ion association with the mono-anion of a dimeric lactam which is naturally less reactive than a free lactam anion. The velocity of the S_N2 reaction, Eq. (7), is thus decreased. However, the decomposition velocity of the methyldiazonium ion, Eq. (6a), is constant and, hence, the S_N1 character of the reaction is increased which favors *O*-methylation. It is possible that this effect is also involved in "kinetic dependence": investigations[125] have shown that with higher saccharin concentrations more *O*-methylsaccharin is formed.

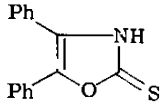
The effect of solvents on the reactions of lactams with diazomethane can be pronounced: saccharin gives only *N*-methyl derivative in benzene solution, but in ethereal solution up to 24% of *O*-methyl saccharin is formed; in the still more strongly polar solvent di-

[124] F. Klages, "Lehrbuch der organischen Chemie," Vol. II, p. 232. W. de Gruyter, Berlin, 1957.
[125] E. Noppel, Diplomarbeit Techn. Hochschule Stuttgart, 1960.

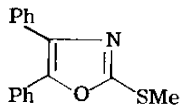
methylformamide the proportion of *O*-methylsaccharin increases to almost 50%.[43]

C. Methylation of Thiolactams

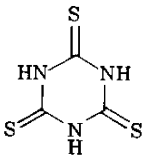
In general the high nucleophilicity of sulfur dominates the reactions of thioamides and thiolactams with electrophilic reagents. In agreement with this the reaction of 4,5-diphenyloxazoline-2-thione (**35**) with diazomethane in ether gives 92% of 2-methylmercapto-4,5-diphenyloxazole (**36**)[126] and that of benzimidazoline-2-thione yields 72% of 2-methylmercaptobenzimidazole.[45] However, thiolactams which are analogous to phthalimide (i.e., carrying an *N*-substituent which diminishes the mesomerism within the thiolactam group)



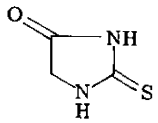
(35)



(36)



(37)



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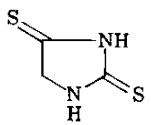

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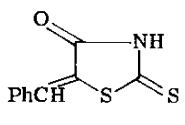


(40)

would be expected to favor *N*-methylation because of the higher nucleophilicity of the nitrogen. A first piece of evidence for this was the observation that in the trimethyl derivative from thiocyanuric acid (**37**) and diazomethane, the methyl groups are partly on the sulfur and partly on the nitrogen.[91] *S*- and *N*-methyl derivatives can both be isolated from 2-thiohydantoins (**38**)[127] and 2,4-dithiohydantoins (**39**).[128] In the case of 5-benzalrhodanine (**40**) only the *N*-methyl derivative[128a] is formed. The methylation of 2-thio-6-azauracil, 4-thio-6-azauracil, and 2,4-dithio-6-azauracil with diazomethane (in

[126] R. Gompper, *Chem. Ber.* **89**, 1762 (1956).
[127] H. C. Carrington, C. H. Vasey, and W. S. Waring, *J. Chem. Soc.* p. 3105 (1953).
[128] H. C. Carrington and W. S. Waring, *J. Chem. Soc.* p. 354 (1950).
[128a] D. J. Dijksman and G. T. Newbold, *J. Chem. Soc.* p. 1213 (1951).

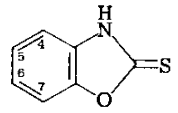
contrast to that with MeI/OH⁻), occurs initially at nitrogen.[128b] Excess diazomethane then causes *S*-methylation.

The results of the methylation of substituted benzoxazoline-2-thiones with diazomethane in ether[129,130] (see Table III) are especially

TABLE III
Methylation of Benzoxazoline-2-thiones with Diazomethane in Ether[130]

Compound	Yield (%)	
	N-Methyl	*S*-Methyl
Benzoxazoline-2-thione	3.5	78.0
5-Nitrobenzoxazoline-2-thione	6.1	77.3
7-Nitrobenzoxazoline-2-thione	8.0	75.7
6-Nitrobenzoxazoline-2-thione	17.6	68.1
4-Nitrobenzoxazoline-2-thione	64.7	11.9

illuminating in this connection. Whereas benzoxazoline-2-thione (**41**) and its 5- and 7-nitro derivatives only undergo a very small proportion of *N*-methylation, the amount of *N*-methylation is noticeably higher in the case of the 6- and especially the 4-nitro derivative. In the two last cases conjugation occurs between the nitro group and the



(41)

free electron pair on the nitrogen. In the other compounds only the inductive effect of the nitro group is operative. The especially high yield of 3-methyl-4-nitrobenzoxazoline-2-thione is also an additional piece of evidence for the field effect of polar groups.

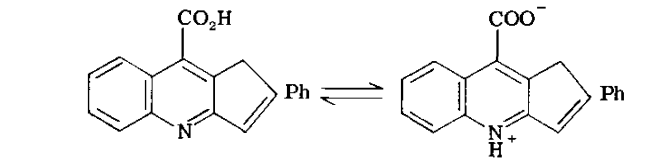
D. Methylation of Heterocyclic Amino Compounds

1. *Cyclic Enamines*

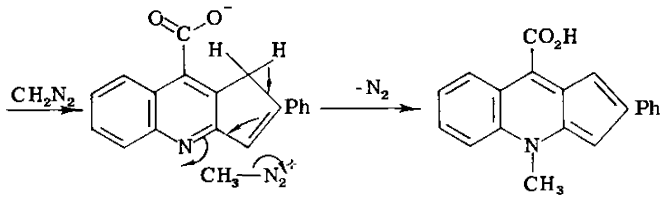
The indole derivative corynantheine is *N*-methylated by diazomethane in ether.[131]

[128b] J. Gut, M. Prystaš, and J. Jonáš, *Collection Czechoslov. Chem. Communs.* **26**, 986 1961).
[129] H. Zinner and K. Niendorf, *Chem. Ber.* **89**, 1012 (1956).
[130] H. Zinner, R. Reimann, and A. Weber, *Chem. Ber.* **93**, 2035 (1960).

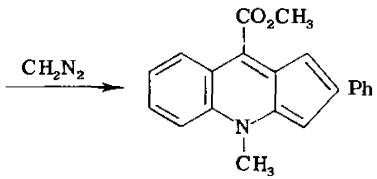
The methylation of 2-phenyl-β-quinindene-9-carboxylic acid (**42**)[132] takes an interesting course (see reaction scheme **42** → **46**). In addition



(**42**) (**43**)



(**44**) (**45**)



(**46**)

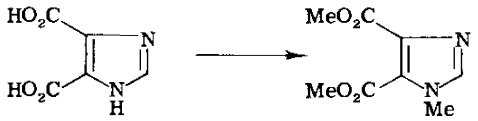
to the methyl ester, methyl 4-methyl-2-phenyl-β-quinindene-9-carboxylate (**46**) is also formed. Because methyl 2-phenyl-β-quinindene-9-carboxylate does not react further with diazomethane, the reaction course (**42** → **46**) must be assumed, i.e., the formation of the zwitterion (**43**) and *N*-methylation by means of the ion pair (**44**). In agreement, the borofluorates of pyridine, quinoline, and isoquinoline are converted by diazomethane to the *N*-methyl quaternary salts.[132a]

2. *Heterocycles with Endocyclic Amidine Groups*

a. Imidazoles. Although the pK_a values of imidazoles[133] [imidazole, 14.52; 2-phenylimidazole, 13.32; 4(5)-phenylimidazole, 13.42] are

[131] A. Chatterjee and P. Karrer, *Helv. Chim. Acta* **33**, 802 (1950).
[132] M. Los and W. H. Stafford, *J. Chem. Soc.* p. 1680 (1959).
[132a] R. Daniels and Ch. G. Kormendy, *J. Org. Chem.* **27**, 1860 (1962).
[133] R. Walba and R. W. Isensee, *J. Org. Chem.* **26**, 2789 (1961).

already somewhat higher than the limit given for lactams to react with diazomethane, various imidazoles do react. Imidazole-4,5-dicarboxylic acid (**47**), for example, yields dimethyl 1-methylimida-



(**47**) (**48**)

zole-4,5-dicarboxylate (**48**).[134] If the substitution in positions 4 and 5 is unsymmetrical, then the methylation can lead to formation of two isomers (see Table IV).

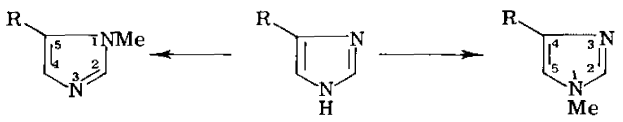
TABLE IV
METHYLATION OF IMIDAZOLES WITH DIAZOMETHANE

Imidazole	Yield (%) 1,5-Derivative[a]	1,4-Derivative[a]
4(5)-Phenyl-[135]	20	41
4(5)-Nitro-[135]	58	1.3
2,4(2,5)-Di*bromo*-5(4)-methyl-[135]	63	6.3
2-Methyl-4(5)-amino-5(4)-*ethoxycarbonyl*[11]	84	—

[a] Position of the methyl group introduced with respect to the substituent italicized.

An interpretation of the predominant formation of 1,5-derivatives on methylation (**50** → **49**) follows. The imidazole and diazomethane first yield an ion pair; if R is a group with a high electron density (NO_2, CO_2R, Br), the methyldiazonium ion will be near the nitrogen atom adjacent to the R group. In these cases methylation is favored in the 5-position. As is shown by the reaction of the imidazoles with dimethyl sulfate and alkali,[136] the adjacent N-atom is probably also somewhat more strongly nucleophilic in the anion than the "distant" nitrogen atom. In the case of 4(5)-phenylimidazole, the phenyl group

[134] R. A. Baxter and F. S. Spring, *J. Chem. Soc.* p. 232 (1945).
[135] W. G. Forsyth and F. L. Pyman, *J. Chem. Soc.* **127**, 573 (1925).
[136] K. Hofmann, "Imidazole and Its Derivatives," Part I, p. 29. Interscience, New York, 1953.



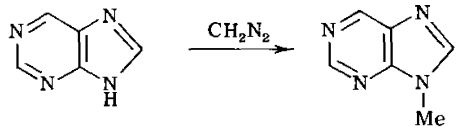
(49) (50) (51)

apparently offers steric hindrance to attack on the "adjacent" nitrogen atom, and the predominant path is **50** → **51**.

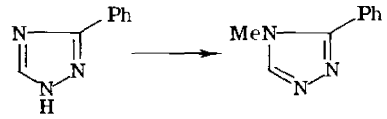
This mechanism does not require a decision as to the question of whether the association of imidazole occurs through hydrogen bonding or by ionization.[137] However, if the methylation with diazomethane is considered together with methylations with dimethyl sulfate, dimethyl sulfate and alkali, and methyl iodide and the silver derivative of the imidazole, then such a comparison is best done using the hydrogen-bonded association model.

From purine (**51a**), 9-methyl purine (**51b**) is formed.[137a]

b. Triazoles. 3(5)-Phenyl-1,2,4-triazole (**52**) is converted by diazomethane into 1-methyl-5-phenyl-1,2,4-triazole (**53**).[138]



(51a) (51b)

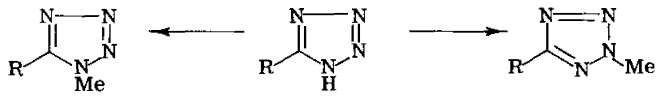


(52) (53)

c. Tetrazoles. 5-Bromo- and 5-amino-tetrazole (**55**) give with diazomethane mixtures of the 5-substituted 1-methyl- (**54**) and 2-methyltetrazoles (**56**).[100] 5-Ethoxycarbonyltetrazole, in which the nitrogen atom at the 1-position is conjugated with the carbethoxy group and,

[137] W. Otting, *Chem. Ber.* **89**, 2887 (1956).
[137a] H. Bredereck, H. Ulmer, and H. Waldmann, *Chem. Ber.* **89**, 12 (1956).
[138] M. R. Atkinson and J. B. Polya, *J. Chem. Soc.* p. 3319 (1954).

therefore, has an electron deficiency, is converted solely to 2-methyl-5-ethoxycarbonyltetrazole (**56**, R = CO_2Et).[139] In the case of 5-(*N*-

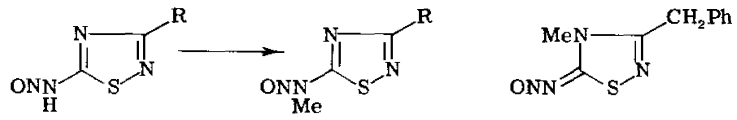


(54) (55) (56)

methylbenzylamino)tetrazole, by contrast, the exclusive formation of the 1-methyl derivative (cf. **54**) is described.[140]

3. Heterocycles with a Semicyclic Amidine Group

5-Nitrosamino-3-phenyl-1,2,4-thiodiazole and the corresponding 3-methyl derivative (**57**, R = Ph,Me) give with diazomethane, 5-(methylnitrosamino) derivatives (**58**).[141] From 5-nitrosamino-3-benzyl-1,2,4-thiodiazole (**57**, R = $PhCH_2$), by contrast, some 5-nitrosimino-4-methyl-3-benzyl-1,2,4-thiodiazoline (**59**) is also pro-

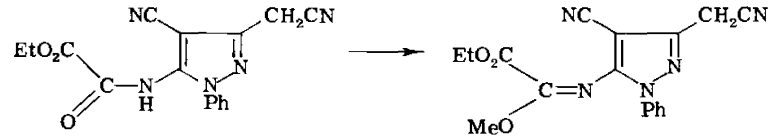


(57) (58) (59)

duced. The yields are, however, rather poor, especially for the conversion of 5-nitrosamino-1,2,4-thiodiazole into 4-methyl-5-nitrosimino-1,2,4-thiodiazoline.

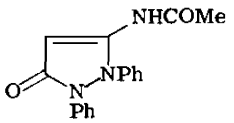
4. Heterocycles with Exocyclic Amino Groups

The reaction of 1-phenyl-3-cyanomethyl-4-cyano-5-(ethyloxalylamino)pyrazole (**60**) with diazomethane in tetrahydrofuran–ether at

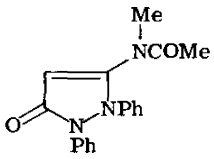


(60) (61)

[139] O. Gryszkiewicz-Trochimowski, *Compt. rend. acad. sci.* **246**, 2627 (1958); *Chem. Abstr.* **54**, 3394 (1960).
[140] R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.* **76**, 923 (1954).
[141] J. Goerdeler and K. Deselaers, *Chem. Ber.* **91**, 1025 (1958).



(62)

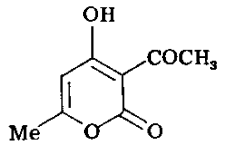


(63)

0°C gives in 52% yield 1-phenyl-3-cyanomethyl-4-cyano-5-(ethoxycarbonylmethoxymethyleneamino)pyrazole (**61**).[142] The *O*-methylation is probably a consequence of steric hindrance by the adjacent groups (CN and C_6H_5). 3-Acetamido-1,2-diphenylpyrazolin-5-one (**62**) is, by contrast, converted to 3-(*N*-methylacetamido)-1,2-diphenylpyrazolin-5-one (**63**), i.e., it undergoes *N*-methylation.[143] 2-(Arylsulfonylamino)-thiazoles and -pyridines[143a] are methylated by diazomethane both on the 2-amino-group and on the ring nitrogen atom (see also footnote 143b).

E. Methylation of Heterocyclic Enols

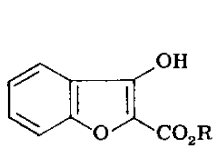
As expected, heterocyclic enols and potential enols (i.e., compounds existing mainly in the CH form) behave toward diazomethane similarly to the open chain and isocyclic enols, i.e. they form enol methyl ethers by reactions of the S_N1 type (cf. footnote **29**). Examples of this behavior are: barbituric acid,[84] pierolonic acid,[125] dehydroacetic acid (**64**),[125] 3-methyl-1-phenylpyrazolin-5-one,[36] 1-phenylpyrazolidine-3,5-dione,[61] 1,2-diphenylpyrazolidine-3,5-dione,[144] 3-hydroxy-



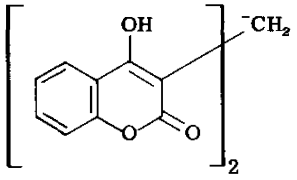
(64)

[142] E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2456 (1959).
[143] M. A. McGee, G. T. Newbold, J. Redpath, and F. S. Spring, *J. Chem. Soc.* p. 2536 (1960).
[143a] R. G. Shepherd, A. C. Bratton, and K. C. Blanchard, *J. Am. Chem. Soc.* **64**, 2532 (1942).
[143b] H. Dorn, G. Hilgetag, and A. Rieche, *Angew. Chem.* **73**, 561 (1961).
[144] L. Capuano, *Chem. Ber.* **92**, 2674 (1959). See also reference in footnote 143.

benzofuran-2-carboxylate esters (**65**),[145] dicoumarol (**66**),[146] 3-phenylisoxazolin-5-one,[147] 3-phenyl-4-cyanoisoxazolin-5-one,[148] 4-ethoxycar-



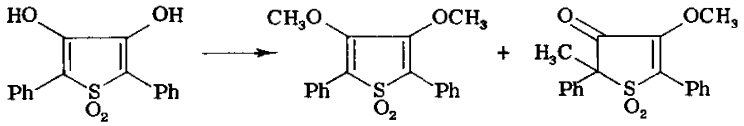
(65)



(66)

bonylisoxazolin-5-one,[125] acetonedicarboxylic anhydride,[149] and "tetrinic acid."[149a]

In systems in which the mesomerism is interfered with, *C*-methylation can also occur. For example, this is shown by the reaction of 3,4-dihydroxy-2,5-diphenylthiophene-1,1-dioxide (**67** → **68** + **69**).[150]

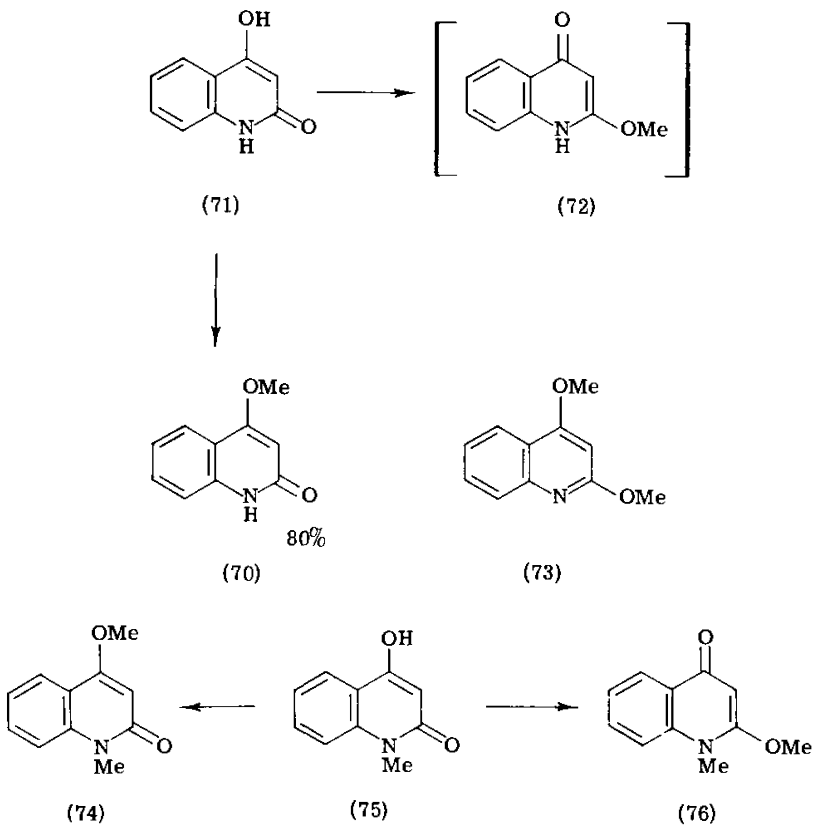


(67) (68) (69)

The methylation of 4-hydroxyquinol-2-one (**71**)[94] is interesting. This compound is both an enol and a lactam; it forms 80% of 4-methoxyquinol-2-one (**70**) and 20% of 2,4-dimethoxyquinoline (**73**). The dimethoxy compound must be formed from 2-methoxyquinol-4-one (**72**) because 4-methoxyquinol-2-one (**70**) does not react with diazomethane. 4-Hydroxy-1-methylquinol-2-one (**75**) yields a mixture of the 4-methoxy analog (**74**) and 2-methoxy-1-methylquinol-4-one (**76**): the proportions of the products show "kinetic dependence" on the concentration of the diazomethane.

The reactions in the 4-hydroxypyranone series are similar to those

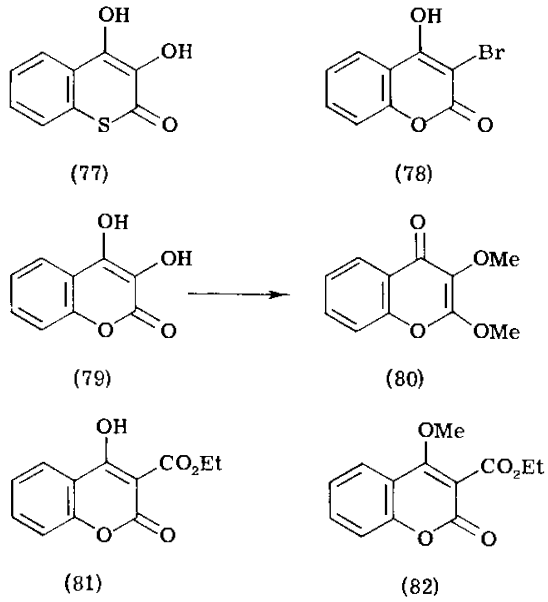
[145] I. Forsblad, *Arkiv Kemi* **13**, 349 (1958); *Chem. Abstr.* **53**, 17112 (1959).
[146] I. Chmielewska and J. Cieślak, *Tetrahedron* **4**, 135 (1958).
[147] E. Oliveri-Mandalà and A. Coppola, *Atti reale accad. Lincei* (I) **20**, 248 (1911).
[148] A. Dornow and H. Teckenburg, *Chem. Ber.* **93**, 1103 (1960).
[149] J. Lityński and R. Malachowski, *Roczniki Chem.* **7**, 579 (1927); *Chem. Abstr.* **22**, 4124 (1928).
[149a] F. Pelizzoni and G. Jommi, *Gazz. chim. ital.* **89**, 1894 (1959); *Chem. Abstr.* **55**, 5338 (1961).
[150] C. G. Overberger and J. M. Hoyt, *J. Am. Chem. Soc.* **73**, 3305 (1951).



for the 4-hydroxyquinol-2-ones. As already mentioned, the "kinetic dependence" was observed for the first time with 5-methylthiocoumarin-3,4-diol[123] (**77**). However, the effect was only somewhat later recognized as such.[151] (For the process of "direct" methylation in the case of enols see *inter alia* reference **152**). Further examples are the methylation of thiocoumarin-3,4-diol,[153] 4-hydroxycoumarin,[154,155] 4-hydroxy-3-bromocoumarin (**78**),[154,156] 3-chloro- and 3-acetamido-4-

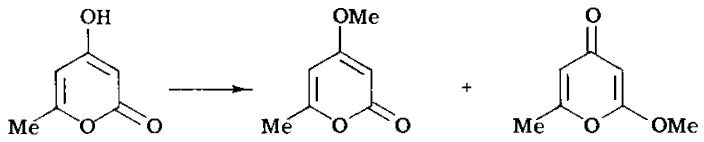
[151] F. Arndt and B. Eistert, *Ber. deut. chem. Ges.* **68**, 1572 (1935).
[152] B. Eistert, F. Arndt, L. Loewe, and E. Ayca, *Chem. Ber.* **84**, 165 (1951).
[153] F. Arndt, L. Loewe, and E. Ayca, *Chem. Ber.* **84**, 329 (1951).
[154] F. Arndt, L. Loewe, R. Ün, and E. Ayca, *Chem. Ber.* **84**, 319 (1951).
[155] I. M. Heilbron and D. W. Hill, *J. Chem. Soc.* p. 1707 (1927).
[156] C. F. Huebner and K. P. Link, *J. Am. Chem. Soc.* **67**, 99 (1945).

hydroxycoumarin.[154] The strong dependence of the methylation on the structure is shown by the fact that coumarin-3,4-diol (**79**)[154] gives only 2,3-dimethoxychromone (**80**) but that 4-hydroxy-3-ethoxycarbonylcoumarin (**81**)[154] forms exclusively the 4-methoxy analog (**82**).



Divergent reports are available regarding the action of diazomethane on triacetic acid lactone (**83**). In the first investigations the sole formation of 6-methyl-2-methoxypyran-4-one (**85**)[157] or of 6-methyl-4-methoxypyran-2-one (**84**)[158] was reported. Later it was shown that a mixture of both compounds is formed albeit the 2-methoxy derivative (**85**) in small yield.[159-162] The discrepancies are in

[157] F. Arndt and S. Avan, *Chem. Ber.* **84**, 343 (1951).
[158] R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.* **78**, 624 (1956).
[159] I. Chmielewska and J. Cieślak, *Przemysł Chem.* **8**, 196 (1956). I. Chmielewska, J. Cieślak, and T. Kraczkiewicz, *Roczniki Chem.* **30**, 1009 (1956); *Chem. Abstr.* **51**, 8733 (1957).
[160] S. Janiszewska-Drabarek, *Roczniki Chem.* **27**, 456 (1953); *Chem. Abstr.* **49**, 3176 (1955).
[161] D. Herbst, W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Am. Chem. Soc.* **81**, 2427 (1959).
[162] J. D. Bu'Lock, and H. G. Smith, *J. Chem. Soc.* p. 502 (1960).



(83) (84) (85)

part explained (see the preceding) because the reaction course depends on the way in which the diazomethane is added. As can be seen from Table V, the proportion of the 2-methoxy compound increases with the rate of addition of diazomethane.[163]

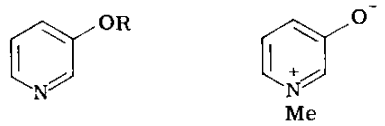
TABLE V
METHYLATION OF TRIACETIC ACID LACTONE WITH DIAZOMETHANE IN ETHER[163]

Time of addition of CH_2N_2 (hr)	Yield (%) 2-Methoxy-	4-Methoxy-
Rapid	0	100
2–4	26	74
18	33	67

The interpretation of the "kinetic dependence" by hydroxypyranones, -coumarins, -thiocoumarins, and -quinolones must depend on the fact that in the corresponding anions the oxygen at C-4 is more nucleophilic than that at C-2. This is shown in the methylation of triacetic acid lactone with dimethyl sulfate and sodium hydroxide.[161,162] Because of the adjacent ring hetero atom, the electron density is, on the other hand, probably higher at O-2 than at O-4. At higher diazomethane concentrations, the formation of the 4-methoxy derivatives is thus favored (greater S_N2 character of the reaction) and with smaller diazomethane concentrations the 2-methoxy derivative tends to be formed. The methylation at O-2 is probably also favored because the mesomeric anion is stabilized by means of unreacted enol (see the preceding). (According to Arndt, the occurrence of the 2-methoxy compound is attributed to the greater acidity of the 2-hydroxy tautomer which it is assumed occurs in small concentration.)

[163] H. Nakata, S. Takahashi, K. Yamada, and Y. Hirata, *Tetrahedron Letters* No. 16, 9 (1959); *Chem. Abstr.* **54**, 4557 (1960).

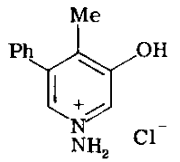
3-Hydroxypyridine (**86**, R = H) and its derivatives also belong to the class of heterocyclic enols. In benzene and dioxane, 3-hydroxypyridine occurs as the neutral molecule (and not as a betaine).[164] Its reaction with diazomethane, in heterogeneous media, gives a mixture of 3-methoxypyridine (**86**, R = Me) (10%) and 1-methyl-3-hydroxypyridinium betaine (**87**) (30%).[55,165] If *tert*-butanol is used as a



(86) (87)

solvent at from −15 to −20°C, then 3-methoxypyridine is formed in 73% yield.[165] Higher temperatures decrease the yield of methoxy derivative (see also footnotes 99 and 166). From 3-hydroxy-4-methyl-5-phenylpyridine the 3-methoxy compound is formed similarly.[167]

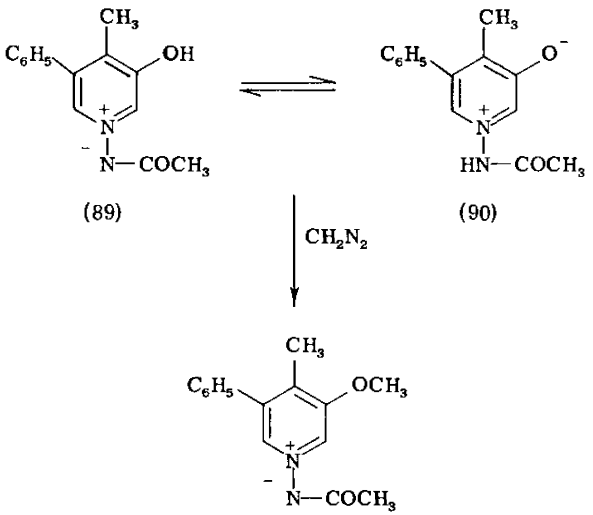
3-Hydroxypyridine 1-oxide is methylated at the 3-hydroxyl group[165,167] just as is 3-hydroxypyridine. On the other hand, 3-hydroxy-1-amino-4-methyl-5-phenylpyridinium chloride (**88**) gives



(88)

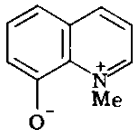
only 1-amino-3-hydroxy-4-methyl-5-phenylpyridinium betaine by elimination of hydrogen chloride.[168] *O*-Methylation at the 3-position occurs again for 1-acetamido-3-hydroxy-4-methyl-5-phenylpyridinium betaine (**89** ⇌ **90**).[168] These results are also noteworthy because the acids corresponding to (**89**) and (**90**) have pK_a values of 4.2 and 6.3 for the NH and OH groups, respectively.

[164] D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc.* **77**, 2431 (1955).
[165] D. A. Prins, *Rec. trav. chim.* **76**, 58 (1957).
[166] L. Marion and W. F. Cockburn, *J. Am. Chem. Soc.* **71**, 3402 (1949).
[167] J. A. Moore and H. H. Püschner, *J. Am. Chem. Soc.* **81**, 6041 (1959).
[168] J. A. Moore and J. Binkert, *J. Am. Chem. Soc.* **81**, 6045 (1959).



(89) (90)

In this connection the conversion of 8-hydroxyquinoline to 1-methyl-8-hydroxyquinolinium betaine (**91**)[169-172] should also be men-



(91)

tioned. A small amount of 8-methoxyquinoline is isolated as a by-product.

II. Other Reactions of Diazomethane with Heterocycles

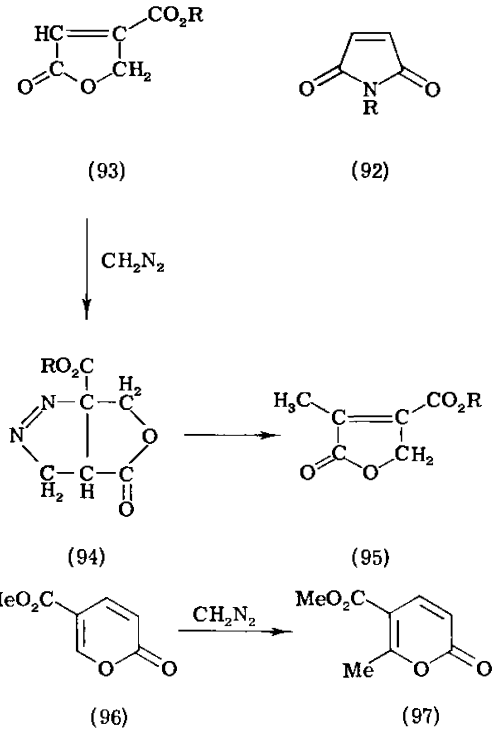
A. Reaction with C=C Double Bonds

Heterocycles with "olefinic" C=C double bonds are able to add diazomethane to form pyrazolines, for example, maleic acid imide,[61,172]

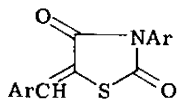
[169] H. and M. Schenkel-Rudin, *Helv. Chim. Acta* **27**, 1456 (1944).
[170] J. P. Phillips and R. W. Keown, *J. Am. Chem. Soc.* **73**, 5483 (1951).
[171] G. Caronna and B. Sansone, *Gazz. chim. ital.* **69**, 24 (1939).
[172] F. Arndt, *Rev. fac. sci. univ. Istanbul* **A9**, 19 (1944).

N-arylmaleic acid imides (**92**)[173] and aconic acid (**93**)[174] react in this way.

The "*C*-methylation" of methyl pyran-2-one-5-carboxylate (**96**) to methyl 6-methylpyran-2-one-5-carboxylate (**97**)[175] can be in-



(93) (92) (94) (95) (96) (97)



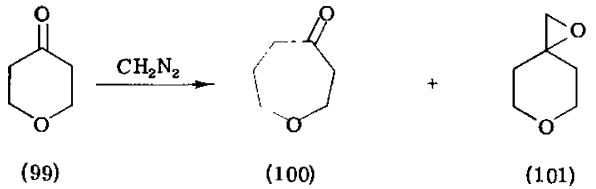
(98)

[173] A. Mustafa, S. M. A. D. Zayed, and S. Khattab, *J. Am. Chem. Soc.* **78**, 145 (1956).
[174] R. F. Rekker, J. P. Brombacher, and W. Th. Nauta, *Rec. trav. chim.* **73**, 417 (1954).
[175] J. Fried and R. C. Elderfield, *J. Org. Chem.* **6**, 577 (1941).

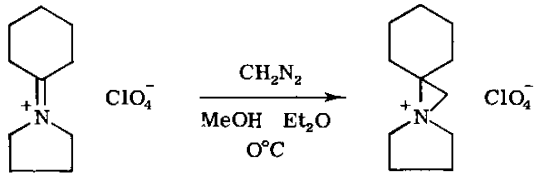
terpreted on the basis of the formation of an unstable pyrazoline (see footnote 3) in analogy with the conversion (**94**→**95**). The *C*-methylation of 5-arylidene-3-arylthiazolidine-2,4-diones (**98**)[176] can be clarified similarly.

B. Reactions with C=X Double Bonds

The reactions of diazomethane with heterocycles containing a ketonic grouping in the ring do not differ, in principle, from those of alicyclic ketones (see footnotes 3 and 177): ring expansion and the formation of epoxides compete. In general, ring expansion is the more important reaction; for example, tetrahydropyran-4-one (**99**) is converted to 1-oxacycloheptan-4-one (**100**) (60%) and 4,4′-epoxy-4-methyltetrahydropyran (**101**) (23%).[178]



(99) (100) (101)



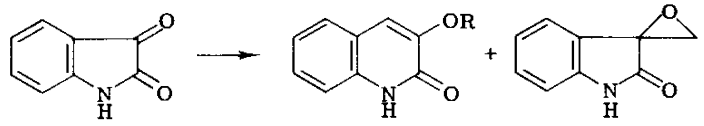
(101a) (101b)

The reaction with *N*-cyclohexylidenepyrrolidinium perchlorate (**101a**) is particularly interesting: 2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate (**101b**) is formed in 88% yield.[178a]

The reactions of heterocyclic 1,2-dicarbonyl compounds with diazomethane, which were studied by Eistert and his co-workers in

[176] A. Mustafa, W. Asker, and M. Ezz El-Din Sobhy, *J. Am. Chem. Soc.* **82**, 2597 (1960).
[177] C. D. Gutsche, *Org. Reactions* **8**, 364 (1954).
[178] S. Olsen and R. Bredoch, *Chem. Ber.* **91**, 1589 (1958).
[178a] N. J. Leonard and K. Jann, *J. Am. Chem. Soc.* **82**, 6418 (1960); *idem, ibid.* **84**, 4806 (1962).

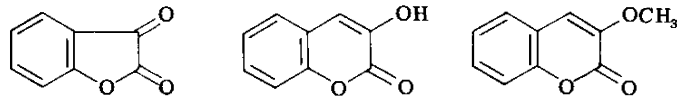
connection with their investigations on orthoquinones, are of especial interest. Isatin (**102**) reacts with diazomethane to give 3-hydroxy- (**103**, R = H) and 3-methoxy-carbostyril (**103**, R = Me)[179]; 3,3′-epoxy-3-methyloxindole (**104**) is formed as a by-product. Only 3-



(102) (103) (104)

hydroxy- and 3-methoxy-1-methylcarbostyril could be isolated from the reaction of *N*-methylisatin with diazomethane.[180-182]

The same insertion of a methylene group between a benzene ring and carbonyl group is also found in the reaction of coumarandione (**105**→**106**→**107**).[182] (The reaction course described by Schönberg *et al.*[183] could not be confirmed.[182])

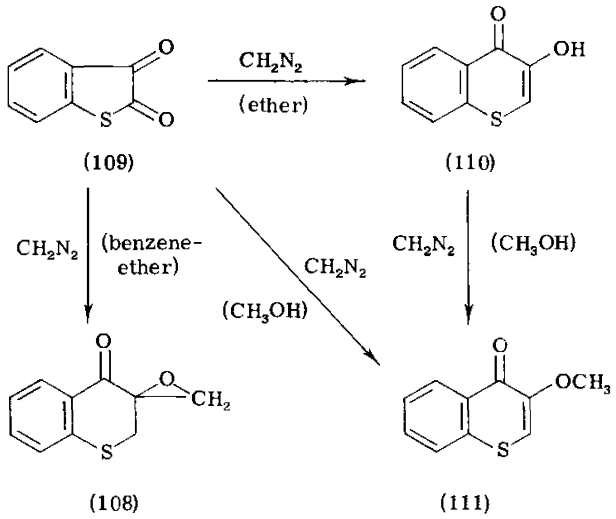


(105) (106) (107)

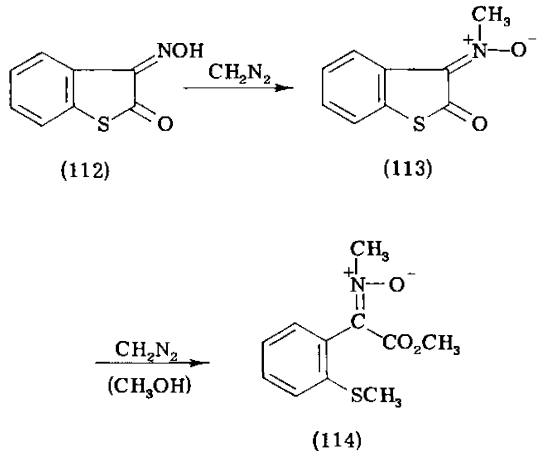
Thianaphthenequinone[182] (**109**) and diazomethane give a different reaction from that found with isatin, *N*-methylisatin and coumarandione. In as far as crystalline products could be isolated, the ring expansion occurs here between the sulfur and the carbonyl group in the 2-position. Depending on the solvent, there are formed 3-hydroxythiochromone (**110**), its *O*-methyl derivative (**111**), or (presumably by attack on the 3-keto group of the tautomeric 3,4-diketo form of **110**), 3,3′-epoxy-3-methylthiochromone (**108**).

The difference in the reaction course for thianaphthenequinone can be explained in the following way[182]: in isatin and coumarandione the carbonyl group in the 3-position is considerably more reactive than

[179] F. Arndt, B. Eistert, and W. Ender, *Ber. deut. chem. Ges.* **62**, 55 (1929).
[180] G. Heller, *Ber. deut. chem. Ges.* **59**, 706 (1926).
[181] R. G. Ault, E. L. Hirst, and R. A. Morton, *J. Chem. Soc.* p. 1653 (1935).
[182] B. Eistert and H. Selzer. H. Selzer, Dissertation, Universität des Saarlandes, Saarbrücken, 1961.
[183] A. Schönberg, R. Moubasher, and A. Mustafa, *J. Chem. Soc.* p. 348 (1941).



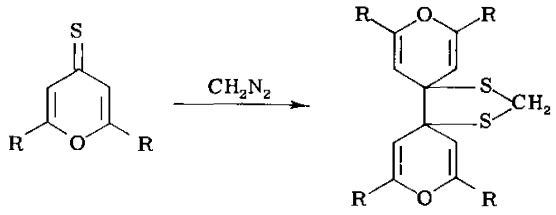
that in the 2-position, which is present as part of a lactam or lactone group in these compounds. In the thiolactone group which occurs in thianaphthenequinone there is only weak mesomerism; the activation of the 2-carbonyl group by the inductive effect of both the sulfur atom and the carbonyl group in the 3-position is more important.



If the carbonyl group in the 3-position of N-methylisatin or thianaphthenequinone is blocked by formation of an oxime (cf. **112**), *N*-methylation of the oxime group occurs instead of ring expansion on reaction with diazomethane. In methanol, thianaphthenequinone oxime *N*-methyl ether (**113**) then undergoes ring opening catalyzed by diazomethane (**113** → **114**).

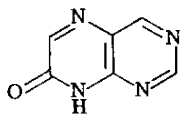
The ring opening reactions of unsaturated azlactones[184] and other lactones[185,186] by methanol in the presence of diazomethane are analogous in principle. (The ring closure of pseudouric acid[187] which occurs under the influence of diazomethane can also be understood as an example of base catalysis.)

Unusual reactions occur between diazomethane and heterocyclic thiocarbonyl compounds. For example, pyran-4-thiones[188] give methylene ethers of 1,2-dimercaptans formed by dimerization (cf. **115** → **116**). 4-Thioflavones[188,189] and 4-thiochromones[188,190] react similarly.

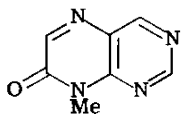


"Normal reactions" are found again for systems containing C=N double bonds. An unstable triazoline is probably an intermediate product in the reaction of pteridin-7-one (**117**)[70] to give a mixture of the 8-methyl (**118**) and 6,8-dimethyl derivatives (**119**). *C*-Methylation also occurs in the case of quinoxalin-2-one.[69]

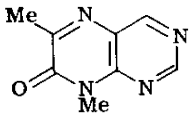
[184] H. Fischer and H.-J. Hofmann, *Z. physiol. Chem., Hoppe Seyler's* **245**, 140 (1937).
[185] E. Y. Spencer and G. F. Wright, *J. Am. Chem. Soc.* **63**, 2017 (1941).
[186] O. Th. Schmidt, H. Zeiser, and H. Dippold, *Ber. deut. chem. Ges.* **70**, 2402 (1937).
[187] H. Biltz and W. Klemm, *Ann.* **448**, 157 (1926).
[188] A. Schönberg, M. Elkaschef, M. Nosseir, and M. M. Sidky, *J. Am. Chem. Soc.* **80**, 6312 (1958).
[189] A. Schönberg and S. Nickel, *Ber. deut. chem. Ges.* **64**, 2323 (1931).
[190] A. Schönberg, H. Kaltschmitt, and H. Schulten, *Ber. deut. chem. Ges.* **66**, 245 (1933).



(117)



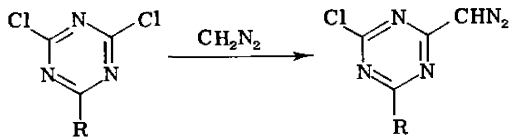
(118)



(119)

C. Reaction with Heterocyclic Halogen Compounds

Because of the high polarity of the C=N double bonds, cyanuric chloride (**120**, R = Cl) is comparable with a carboxylic acid chloride. This explains its smooth reaction with diazomethane to yield dichloro-(diazomethyl)-1,3,5-triazine (**121**, R = Cl).[191,192] The analogous compounds (**120**, R = Me,Ph) react similarly.



(120) (121)

R = Cl, CH_3, C_6H_5

[191] C. Grundmann and E. Kober, *J. Am. Chem. Soc.* **79**, 944 (1957).
[192] J. A. Hendry, F. L. Rose, and A. L. Walpole, *J. Chem. Soc.* p. 1134 (1958).

The Acid-Catalyzed Polymerization of Pyrroles and Indoles

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I. The Acid-Catalyzed Polymerization of Pyrroles

A. General Survey

The action of strong acids on pyrroles very much depends on the nature of the ring substituents. In general, pyrroles containing an electron-withdrawing substituent are either unaffected or form simple proton salts.[1] Polymerization and, under appropriate conditions, further reaction with loss of ammonia, is observed only with pyrrole and some of its simple alkyl and aryl derivatives; many polyalkyl pyrroles, however, form relatively stable monomeric salts with strong acids. Nothing much is yet known about the behavior of pyrrolones and of halogeno-, methoxy-, and amino-pyrroles.

Pyrrole itself is very easily converted by acid into intractable and readily autoxidized polymers. In this case and in the case of the alkyl pyrroles, it is important to distinguish between anaerobic acid-catalyzed reactions and autoxidative polymerizations: the decomposition of pyrrole and its alkyl derivatives on standing in air belongs to the latter type, this review is concerned only with the former.

[1] A. Treibs and H. G. Kolm, *Ann.* **606**, 166 (1957).

Pyrrole, then, polymerizes very readily in acid. By the controlled use of dry HCl in ether[2] or of 6 *N* aqueous HCl for a few seconds,[3,4] variable yields of a homogeneous trimer may be obtained. The isolation of pyrrole dimer has not yet been reported, although what may be a fairly homogeneous complex of dimer and $SnCl_4$ has been described.[5] Attempts to liberate the free base from this complex were unsuccessful.

N-Methylpyrrole also polymerizes readily.[4] A crystalline dimer or trimer has not, however, yet been isolated.

2-Methyl-,[6] 2-isopropyl-,[6] 2,3-dimethyl-,[7,8] 2-methyl-3-ethyl-,[9] and 3-methyl-2-ethyl-pyrrole[10] all form crystalline salts of the corresponding dimers with dry HCl or picric acid in ether; variable quantities of noncrystalline material are also produced. The dimers are quite stable even as the free bases.

3-Methylpyrrole gives only amorphous polymeric material with HCl or picric acid in ether.[11] In contrast with the pyrroles just mentioned, 2,5- and 3,4-dimethyl-,[12] 2-methyl-5-ethyl-,[13] 3-methyl-4-ethyl-,[14] and 2-methyl-4-ethyl-pyrrole[15] do not form crystalline salts, either monomeric or dimeric, and 2,4-dimethyl-[16] and 4-methyl-2-ethyl-pyrrole[17] form only monomeric salts. The dialkylpyrroles in this latter group all dissolve in aqueous sulfuric acid to form relatively stable solutions (e.g., references 14 and 15). The various tri- and tetra-akylpyrroles are likewise soluble in aqueous mineral acid to form stable solutions, and either do not react with HCl or picric acid

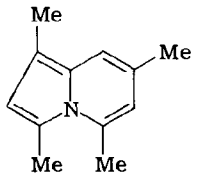
[2] M. Dennstedt and J. Zimmermann, *Ber. deut. chem. Ges.* **21**, 1478 (1888).
[3] M. Dennstedt and F. Voigtländer, *Ber. deut. chem. Ges.* **27**, 478 (1894).
[4] W. Tschelinzew, B. Tronow, and B. Woskressenski, *Chem. Zentr.* **87** (I), 1246 (1916).
[5] O. Schmitz-DuMont, *Ber. deut. chem. Ges.* **62**, 226 (1929).
[6] M. Dennstedt and J. Zimmermann, *Ber. deut. chem. Ges.* **21**, 3429 (1888).
[7] M. Dennstedt, *Ber. deut. chem. Ges.* **22**, 1922 (1889).
[8] O. Piloty and S. J. Thannhauser, *Ann.* **390**, 201 (1912).
[9] O. Piloty, K. Wilke, and A. Blömer, *Ann.* **407**, 37 (1915).
[10] H. Fischer, H. Beller, and A. Stern, *Ber. deut. chem. Ges.* **61**, 1074 (1928).
[11] M. Dennstedt and J. Zimmermann, *Ber. deut. chem. Ges.* **21**, 3439 (1888); O. Piloty and P. Hirsch, *Ann.* **395**, 71 (1913).
[12] H. Fischer and B. Walach, *Ann.* **450**, 129 (1926).
[13] H. Fischer, E. Sturm, and H. Friedrich, *Ann.* **461**, 249 (1928).
[14] O. Piloty and J. Stock, *Ber. deut. chem. Ges.* **46**, 1010 (1913).
[15] H. Fischer and J. Klarer, *Ann.* **450**, 199 (1926).
[16] H. Fischer and E. Bartholomäus, *Z. physiol. Chem. Hoppe-Seyler's* **80**, 14 (1912).
[17] H. Fischer and J. Klarer, *Ann.* **447**, 59 (1926).

in ether or form crystalline monomeric salts. Kryptopyrrole (2,4-dimethyl-3-ethylpyrrole) and phyllopyrrole (2,3,5-trimethyl-4-ethylpyrrole) are exceptional in that they form dimer picrates in hot ethyl acetate.[18]

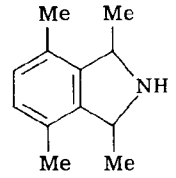
2-Phenylpyrrole is dimerized quite cleanly by HCl in ether.[19]

A reaction of alkylpyrroles with hot aqueous sulfuric acid leading to indoles almost certainly involves the dimers as intermediates,[20] thus 2-methylpyrrole gives 2,4-dimethylindole[6,20] and 2-isopropyl-,[6] 3-methyl-,[11] and 2,3-dimethylpyrrole[7] lead to indoles the structures of which have not yet been established.

Under different conditions, that is in refluxing glacial acetic acid and zinc acetate, 2,4-dimethylpyrrole yields tetramethylpyrrocoline (**1**).[21] Under reducing conditions, with zinc and acetic acid, 2,5-



(1)



(2)

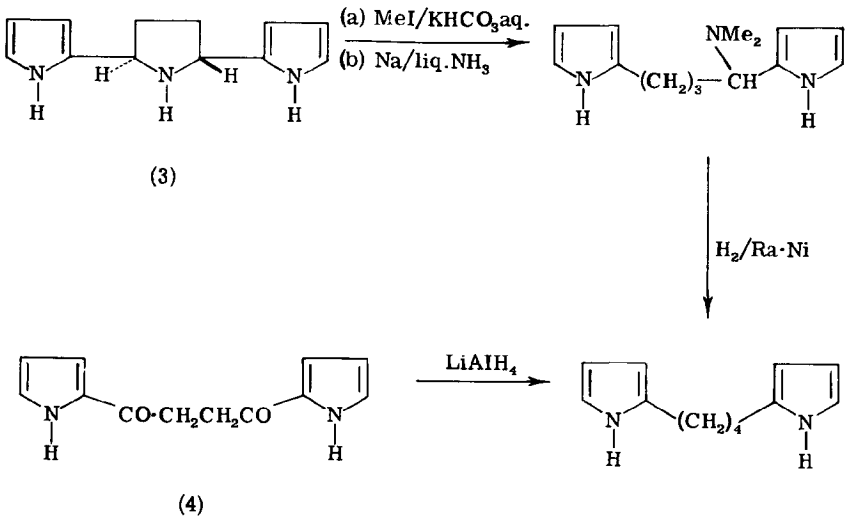
dimethylpyrrole leads to the dihydroisoindole (**2**).[22] 2-Phenylpyrrole is unaffected by hot aqueous mineral acid.[19]

B. Structure of the Individual Oligomers

1. *Tripyrrole*

The correct structure (**3**) for this compound was first proposed in 1922 by Pieroni and Moggi[23] on the basis of the isolation of succinic acid by chromic acid oxidation. Full confirmation of this structure was more recently obtained by Potts and Smith[24] by the degradation outlined in Scheme 1. The dipyrrylbutane was synthesized by the lithium aluminum hydride reduction of the known dipyrrylbutane-

[18] H. Fischer, *Ber. deut. chem. Ges.* **48**, 404 (1915).
[19] C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.* **2**, 227 (1937).
[20] C. F. H. Allen, D. M. Young, and M. R. Gilbert, *J. Org. Chem.* **2**, 235 (1937).
[21] J. E. Saxton, *J. Chem. Soc.* p. 3239 (1951).
[22] R. Bonnett and J. D. White, *Proc. Chem. Soc.* p. 119 (1961); *J. Chem. Soc.* p. 648 (1963).
[23] A. Pieroni and A. Moggi, *Gazz. chim. ital.* (I) **53**, 120 (1923).
[24] H. A. Potts and G. F. Smith, *J. Chem. Soc.* p. 4018 (1957).



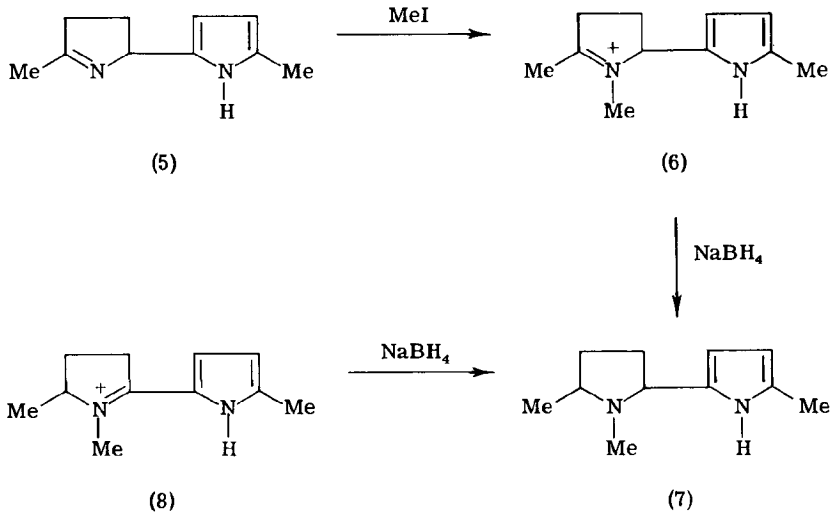
SCHEME 1

dione (**4**). The *trans* relationship of the pyrryl rings in the trimer was demonstrated by Huisgen and Vossius[25] by the isolation of *N*-tosylpyrrolidine *trans*-2,4-decarboxylic acid by chromic acid oxidation of tosyltripyrrole.

2. *2-Methylpyrrole Dimer*

Allen *et al.*[19] mainly on the evaluation of data reported by previous workers, advanced structure (**5**) for 2-methylpyrrole dimer. These data were (*a*) the monobasic nature of the dimer and (*b*) the conversion by aqueous acid into an indole which they showed by elimination (i.e., by the synthesis of 2,5-, 2,6-, and 2,7-dimethylindoles) to be 2,4-dimethylindole (this compound has since been synthesized by Marion and Oldfield[26]). Structure (**5**) for the dimer was confirmed by Edwards and Smith[27] by conversion, by way of the methiodide (**6**), into the pyrrolidinopyrrole (**7**), the structure of which was proved by synthesis: 1,5-dimethylpyrrolid-2-one was condensed with 2-methylpyrrole by means of $POCl_3$ to give the cation (**8**), isomeric with the

[25] R. Huisgen and V. Vossius, personal communication.
[26] L. Marion and C. W. Oldfield, *Can. J. Research* **25B**, 1 (1947).
[27] P. N. Edwards, M.Sc. Thesis, Manchester University, 1958.

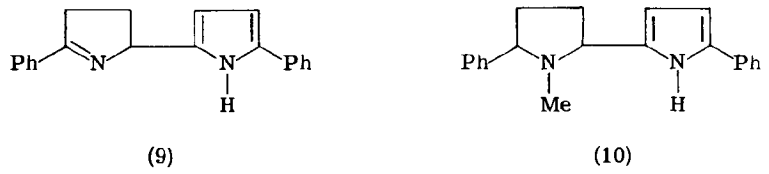


dimer methocation (**6**). Reduction of (**8**) gave (**7**). Ultraviolet and infrared data are in accord with structure (**5**).[27,28]

The structures for 2-isopropyl- and 2,3-dimethyl-pyrrole follow almost certainly by analogy.[19]

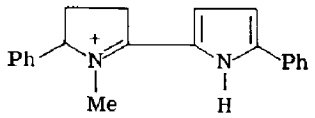
3. *2-Phenylpyrrole Dimer*

This compound was prepared by Allen *et al.*,[19] who found it to be monobasic and to form a simple methiodide. Attempted Hofmann degradation of this methiodide failed to give any information. The dimer was found to be perfectly stable to hot aqueous sulfuric acid. With the foregoing data, and by analogy with the alkyl pyrrole dimers, they proposed structure (**9**) for the dimer. Later work[29] confirmed this structure by conversion via the methiodide into base (**10**) which was synthesized by way of the metho salt (**11**), isomeric with



[28] H. Booth, A. W. Johnson, and F. Johnson, *J. Chem. Soc.* p. 98 (1962).
[29] P. N. Edwards and G. F. Smith, unpublished work (1962).

the dimer metho salt, by a route analogous with that used for the synthesis of (7).

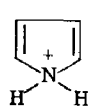


(11)

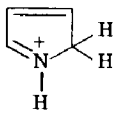
C. Discussion of Possible Mechanisms for the Acid-Catalyzed Polymerization of Pyrroles

1. *Protonation and Polymerization of Pyrrole*

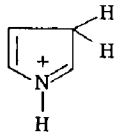
Cations (12), (13), and (14) represent the three ways in which proton may add to pyrrole. Twenty-five years ago, Koizumi and Titani[30] carried out a series of deuterium exchange studies and



(12)



(13)



(14)

showed that the *N*-hydrogen was the only replaceable one down to pH 2. This means that in dilute acid (*N*/100), protonation effectively only occurs on nitrogen, and that protonation on carbon is too slow to be detectable. In stronger acid, exchange of the *C*-hydrogens began to occur, and was rapid at pH 1 (*N*/10), and under these conditions in D_2O all five ring hydrogens were replaced by deuterium. This demonstrates that at strengths of *N*/10 and above, cations (13) and (14) are present in appreciable concentration.

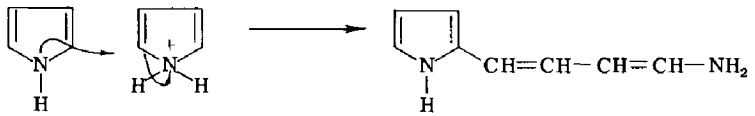
A recent nuclear magnetic resonance (NMR) study of the structure of 2,3,4,5-tetramethyl, 2,3,4- and 2,3,5-trimethyl, and 2,4-dimethylpyrrolium ions in concentrated HCl has shown that they are all protonated on the α-carbon and are thus of type (13).[31]

[30] M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan* **12**, 107 (1937); *ibid.* **13**, 85, 298 (1938).

[31] R. J. Abraham, E. Bullock, and S. S. Mitra, *Can. J. Chem.* **37**, 1859 (1959).

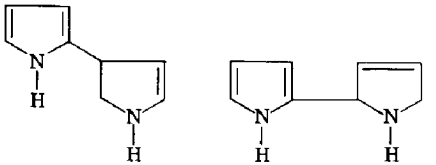
Inspection of the three cations shows that (13) and (14) would be expected to be quite active as electrophilic reagents by reason of delocalization of the positive charge by mesomerism leading to the transfer of electrophilic character to the carbon atom. Cation (12), on the other hand, would show electrophilic reactivity at carbon only by induction. Since neutral pyrrole is so susceptible to electrophilic attack, it is extremely likely that it would react with one or other of the three cations.

Considering each cation in turn, it is difficult to see how cation (12) would react. One could visualize a nucleophilic displacement such as



but the type of molecule thus produced does not seem too likely as an intermediate for tripyrrole.

Cation (13) could react with pyrrole in two ways leading either to (15) or (16). Here again, neither can be seen as a likely intermediate for pyrrole trimer: (15) would lead to the wrong structure, and (16) would be expected to be unreactive, migration of the double



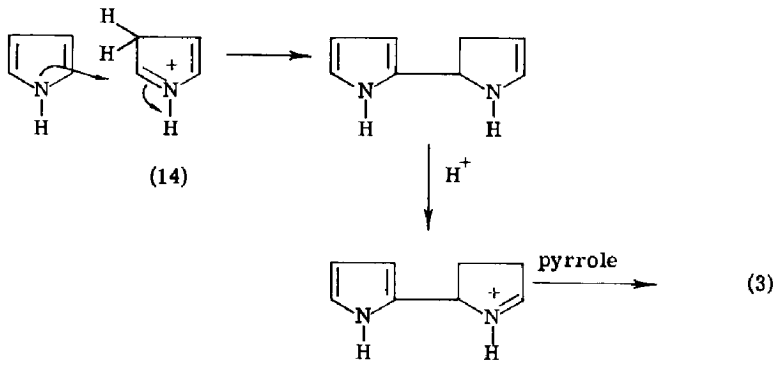
(α-pyrryl)$_2$CH·CH=CH·CH$_2$·NH$_2$

(15) (16) (17)

bond being rendered very unlikely by protonation of the Δ^3-pyrroline nitrogen. At the most, one might expect a reaction of the protonated form to occur in a manner analogous with the formation of indole trimer (see p. 308), leading to (17).

Cation (14) leads straightforwardly to tripyrrole, by way of protonated pyrrole dimer (18), the structure of which corresponds with the structures proved for 2-methyl- and 2-phenyl-pyrrole dimers.

Judging by the predominance of α-substitution in electrophilic attack of pyrrole, one would say that of the cations (13) and (14), the former would greatly predominate. In support of this there is the argument that the charge in (13) is more delocalized (3 canonical



(14) (3)

(18)

forms) than in (**14**) (with only 2 simple canonical forms), thus conferring greater stability to (**13**). Why then is cation (**13**) not involved in the dimerization and trimerization process? The answer must lie in the greater electrophilic reactivity of cation (**14**) which, in spite of being the least abundant, competes successfully with cation (**13**).

The two C—C bond-forming reactions in the trimerization of pyrrole are thus seen to be Mannich-type condensations and find many simple analogies, the most relevant one being that used to prepare 2-2′-pyrrolidinylpyrrole (**19**).[31a]

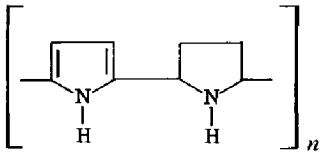
(19)

The trimer having been produced, protonation of the central pyrrolidine nitrogen occurs, and the formal positive charge then sufficiently retards further electrophilic attack on the two pyrrole nuclei to allow the isolation of tripyrrole.

As has been mentioned above, the trimer can only be isolated if very carefully prescribed experimental conditions are followed. The trimer is itself quite a reactive compound and in acid solution, in the

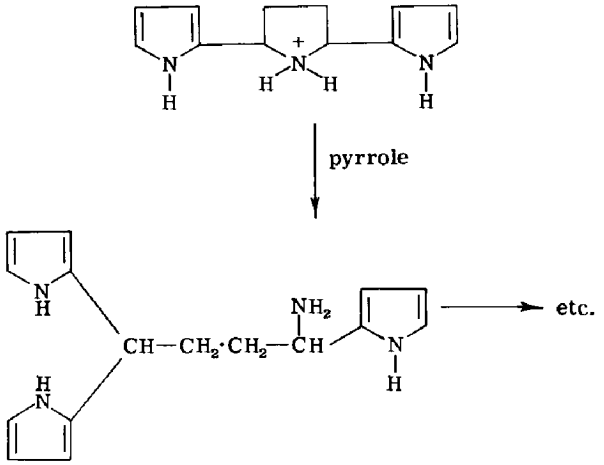
[31a] D. W. Fuhlhage and C. A. Vanderwerf, *J. Am. Chem. Soc.* **80**, 6249 (1958).

presence or absence of pyrrole, undergoes further polymerization. The nature of the higher polymers of pyrrole has not yet been investigated with any success. It is likely that structure (**20**) represents a great

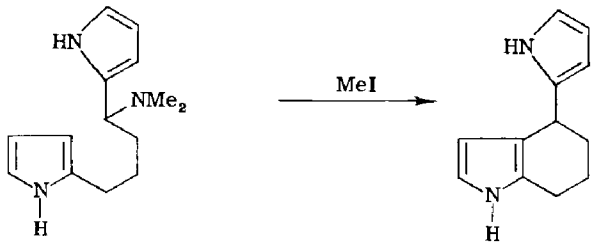


(20)

oversimplification, and that several different types of condensation reactions are occurring side by side leading to a variety of skeletal arrangements. A notable feature of pyrrole polymer is that it is colorless when prepared in the absence of oxygen, but on exposure to air soon turns deep red. This behavior would not be accounted for by structure (**20**); it is, however, reminiscent of the autoxidation of dipyrromethanes to dipyrromethenes. Analogy with indole trimer again offers a working hypothesis,



Further investigation of pyrrole polymer would be of considerable interest. Rather similar to the foregoing hypothetical reaction is the attempted quaternization of (**21**), which leads directly to (**22**), no quaternary salt surviving at all.[24]



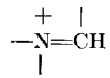
(21) (22)

2. Polymerization of Alkyl Pyrroles

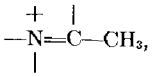
As can be seen from the survey, only a limited number of alkyl pyrroles are polymerized, actually dimerized, by acid in ether or in water. The dimerizable pyrroles include all those which have free adjacent α- and β-positions, that is 2- and 3-methyl-, 2-isopropyl-, and 2,3-dimethyl-pyrrole. It must be repeated that no homogeneous product has yet been obtained from 3-methylpyrrole, and this reaction deserves more study.

The two polyalkylpyrroles which have been reported to form a dimer picrate in refluxing ethyl acetate[18] form an interesting problem, and are briefly discussed on p. 297.

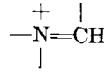
The first question one asks is why does the reaction with 2-methylpyrrole stop at the dimer stage, whereas the pyrrole dimer itself cannot be isolated, but reacts further to form the trimer. The answer probably lies in the greater electrophilic reactivity of



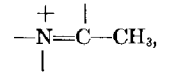
when compared with



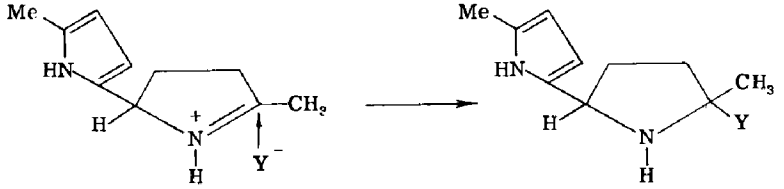
which finds an analogy in the greater reactivity of aldehydes when compared with methylketones. The salt of pyrrole dimer (18) still contains a



group and is thus in a position to attack a further pyrrole molecule, whereas the salt of 2-methylpyrrole dimer (6) contains



which fails to be sufficiently reactive to attack a further 2-methylpyrrole molecule. The reason for this decreased electrophilic reactivity is likely to be in part steric, but probably mainly the consequence of electron release from the methyl group. The steric factor would involve the bringing together of the methyl and pyrryl substituents in a *cis*-1,3 relationship, and this is not likely to cause very marked steric compression.



The failure of 2,5-dimethylpyrrole to dimerize is simple to understand. It is, however, difficult to understand why 2,4- and 3,4-dimethylpyrrole do not form simple dimers.[31]

Nothing is known of the nature of krypto- and phyllo-pyrrole dimers and an investigation of their structure would be of great interest.

D. Discussion of a Possible Free-Radical Mechanism for the Formation of Pyrrole Trimer

Treibs and Kolm[1] have reported that, in the complete absence of oxygen and in the dark, pyrrole dissolves in 1.05 equivalents of 0.75 *N* aqueous HCl—the clear solution is stable for several hours at room temperature and on basification gives unchanged pyrrole in high yield. (This was difficult to achieve, for the authors state that only two out of four experiments succeeded.) It is very difficult to understand how pyrrole, with an extremely low pK_a of the order of zero,[32] can dissolve in 1 equivalent of dilute aqueous acid (1.4 gm pyrrole in 32 ml of aqueous acid). Treibs concludes that protonated pyrrole is stable in solution, and that it is extremely susceptible to autoxida-

[32] N. Naqvi and Q. Fernando, *J. Org. Chem.* **25**, 551 (1960).

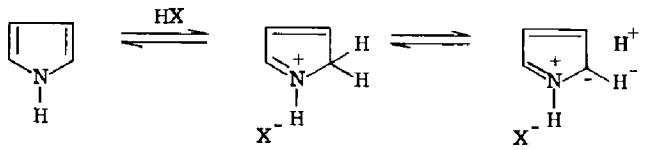
tion. The inference is that polymerization of pyrrole in acid is an autoxidative free-radical process. Acheson,[33] on the basis of the preceding observations, in fact suggests that the trimerization of pyrrole is not a simple acid-catalyzed reaction, but is a free-radical reaction.

The work of Koizumi and Titani[30] shows that down to pH 2 deuterium exchange occurs exclusively at the nitrogen, and that exchange at carbon gradually becomes more significant and is rapid below pH 1. The present author believes that the survival of pyrrole in 0.75 *N* HCl (whether in solution or not) observed by Treibs and Kolm is likely to be the consequence of the low concentration of β-protonated cations, and that the production of trimer in 6 *N* HCl reflects the much higher concentration of the reactive cation in the more strongly acidic medium. It is, in any case, impossible to formulate a plausible free-radical mechanism for the formation of pyrrole trimer. It must be emphasized that only pyrrole trimer formation is being discussed here, concurrent autoxidative polymerization to as yet uncharacterized products is very likely indeed.

Clearly, more experimental work is called for.

E. Treibs' Views on the Nature of the Acid Catalysis of Electrophilic Substitution in Pyrroles

In several papers,[1,34,35] Treibs argues that the effect of acid on the interaction of pyrroles with electrophilic reagents is to increase the susceptibility of the pyrrole nucleus to electrophilic attack: the proton donor is believed to convert the pyrrole nucleus transiently and reversibly into what is described[36] as a salt of an azacyclopentadienyl anion, the activation of the α-position, for example, occurring as follows, (23) being the activated species[34]:



(23)

[33] R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," p. 54. Interscience, New York, 1960.

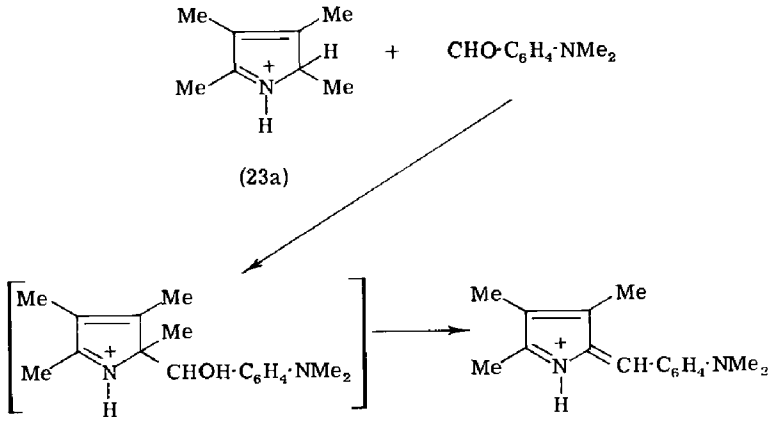
[34] A. Treibs and G. Fritz, *Ann.* **611**, 162 (1958); A. Treibs and H. Bader, *Ann.* **627**, 188 (1959).

[35] A. Treibs, E. Herrmann, E. Meissner, and A. Kuhn, *Ann.* **602**, 163 (1957).

[36] A. Treibs, *Angew. Chem.* **69**, 535 (1957).

In (23) the proton is dissociated from the α-position, whereas the nitrogen still carries the formal positive charge. The dissociated proton remains in the immediate vicinity of the polarized nucleus, as does the anion X^-.

All acid-catalyzed electrophilic substitution reactions are held by Treibs to occur by way of the distinct reactive species (23), thus the very greatly accelerated interaction of pyrrole and formaldehyde in acid solution involves attack of neutral formaldehyde on (23).[1] Another example is the interaction of 2,3,4,5-tetramethylpyrrole with *p*-dimethylaminobenzaldehyde in acid solution, for which the following reaction (Scheme 2) is given,[35] (23a) being presumably intended



SCHEME 2

to be the immediate precursor of a (23) species. (Other instances of this remarkable displacement of a *C*-methyl group under mild conditions have been claimed by Treibs.[36a])

Surely these views are not very plausible, depending as they do on the formation of such an improbable system as (23). How much more simple is it to view acid catalysis as involving enhancement of the electrophilic character of the reagent. Thus, in the formaldehyde condensation, it is protonated formaldehyde,

$$CH_2{=}\overset{+}{O}H,$$

which attacks neutral pyrrole, and likewise it is the *O*-protonated dimethylaminobenzaldehyde which attacks tetramethylpyrrole. Acid

[36a] A. Treibs and H. Derra-Sherer, *Ann.* **589**, 196 (1954).

catalysis here then falls into line with acid-catalyzed aldol condensations, Mannich reactions, etc.

II. The Acid-Catalyzed Polymerization of Indoles

A. General Survey

Indole itself forms a dimer or a trimer, depending on experimental conditions: the dimer hydrochloride is formed in aprotic solvents with dry HCl,[37] whereas aqueous media lead to dimer or trimer, or both.[37–40] It was Schmitz-DuMont and his collaborators who beautifully cleared up the experimental confusion and discovered the simple fact that in aqueous acid the composition of the product is dictated by the relative solubilities of the dimer and trimer hydrochlorides.[41,42] This, of course, established the very important point that there is an equilibrium in solution among indole, the dimer, the trimer, and their salts. It was furthermore demonstrated that the polymerization mechanism involves acid catalysis and that in dilute solution the rate of reaction is dependent on the concentration of acid.

In contrast with pyrrole, the polymerization does not appear to go beyond the trimer stage, any amorphous material produced being the product of autoxidation.

N-Methylindole and 7-methylindole both form dimers and trimers.[43] It was noted that 7-methylindole, in sharp contrast with indole, gave amorphous material in dilute, aqueous, alcoholic HCl from which it was not possible to isolate either dimer or trimer; acetic anhydride reacted with this material to yield a compound $C_{31}H_{33}O_3N_2$ of unknown constitution.

Skatole (3-methylindole) readily forms a dimer hydrochloride with HCl in ether[44] or with 15% aqueous HCl,[45] as does 1,3-dimethylindole.[53] 3-*n*-Propylindole is also readily dimerized in dry ether/HCl.[45]

[37] K. Keller, *Ber. deut. chem. Ges.* **46**, 726 (1913).
[38] M. Scholtz, *Ber. deut. chem. Ges.* **46**, 1082 (1913).
[39] B. Oddo, *Gazz. chim. ital.* (I) **43**, 385 (1913).
[40] O. Schmitz-DuMont and B. Nicolojannis, *Ber. deut. chem. Ges.* **63**, 323 (1930).
[41] O. Schmitz-DuMont, B. Nicolojannis, E. Schnorrenberg, and H. H. Saenger, *J. prakt. Chem.* **131**, 146 (1931).
[42] O. Schmitz-DuMont and H. H. Saenger, *J. prakt. Chem.* **132**, 39 (1931).
[43] O. Schmitz-DuMont and K. H. Geller, *Ber. deut. chem. Ges.* **66**, 766 (1933).
[44] B. Oddo and G. B. Crippa, *Gazz. chim. ital.* (I) **54**, 339 (1924); B. Oddo, *ibid.* **63**, 898 (1933).
[45] G. F. Smith and A. E. Walters, *J. Chem. Soc.* p. 940 (1961).

Schmitz-DuMont's statement[43] that 3-ethylindole does not dimerize must be in error. 3-*tert*-Butyl- and 3-isopropyl-indole and tryptamine do not form dimers,[45] neither does 2-methylindole.[43,44]

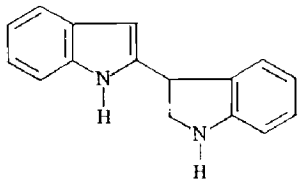
2-Methylindole is, however, incorporated into mixed dimers and trimers. It thus reacts with indole and with skatole to form mixed dimers, and 2 moles react with 1 mole of indole for form a mixed trimer. Likewise indole forms a dimer with 1,2-dimethylindole, 2-phenylindole, and even with 2,5-dimethylpyrrole.[53]

B. Structure of the Individual Oligomers

1. *Indole Dimer*

Mainly based on the failure of 2-methylindole to form a dimer, Schmitz-DuMont proposed structure (**24**) for indole dimer, the argument being that a methyl group in position 2 would effectively hinder the formation of a skeleton of type (**24**), whereas one in position 3 would not.[46,47]

The formation of structure (**24**) is very difficult to rationalize in terms an acid-catalyzed condensation mechanism, but the formation



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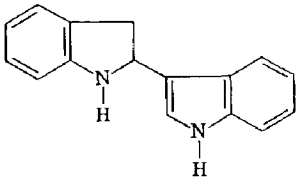


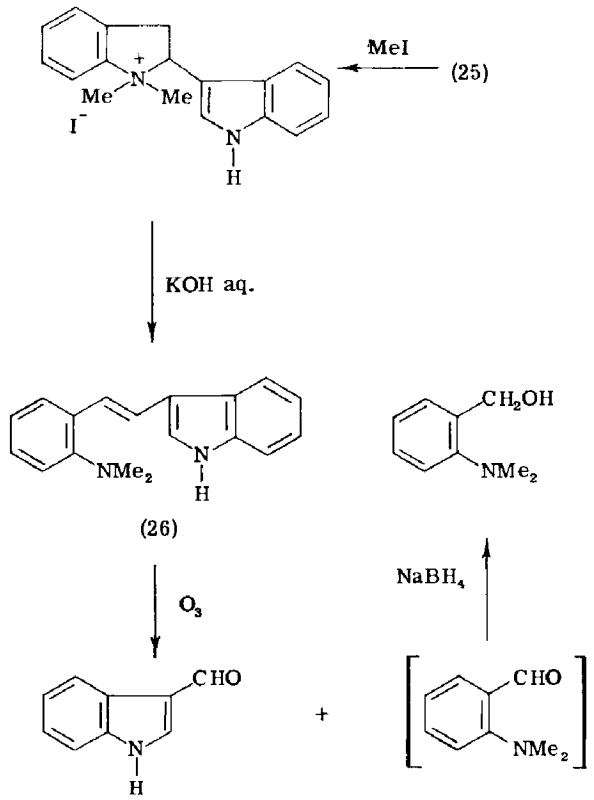
(25)

of structure (**25**), on the other hand, would be very easy. Systematic degradation of indole dimer (Scheme 3) showed that, in fact, (**25**) represents the correct structure.[48]

2. *Indole Trimer*

The structure of this compound followed from the discovery that it contains a primary aromatic amino group.[49] This, together with a simple mechanistic argument, led to the proposal of structure (**27**).

[46] O. Schmitz-DuMont, K. Hamann, and K. H. Geller, *Ann.* **504**, 1 (1933).
[47] O. Schmitz-DuMont, *Ann.* **514**, 267 (1934).
[48] H. F. Hodson and G. F. Smith, *J. Chem. Soc.* p. 3544 (1957).
[49] G. F. Smith, *Chem & Ind. (London)* p. 1451 (1954).

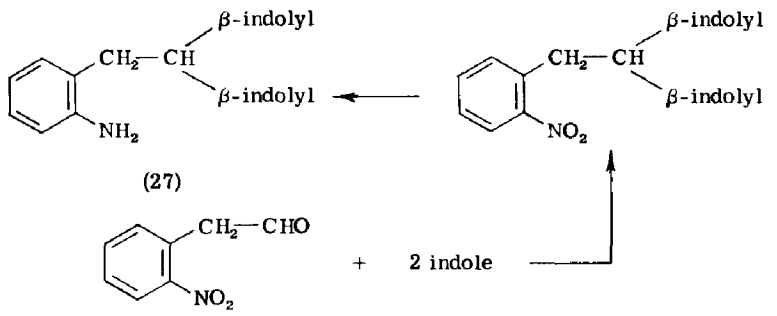


SCHEME 3

This structure rationalizes (a) the formation of mono- and, under more vigorous conditions, tetra-acetyl derivatives, (b) the methylation to a dimethyl derivative still containing two active hydrogens, (c) the pyrolysis back to monomeric indole, (d) the formation of a benzylidene derivative containing the Ph·CH=N—Ar chromophore, (e) the failure to form a simple nitroso derivative, (f) the Zn/AcOH reduction of the dimethyl trimer to base $C_{18}H_{20}N_2$, shown to be identical with the dihydro derivative of (**26**).

Structure (**27**) was confirmed by a very neat synthesis by Noland and Kuryla[50] involving the condensation of the extremely labile

[50] W. E. Noland and W. C. Kuryla, *J. Org. Chem.* **25**, 486 (1960).

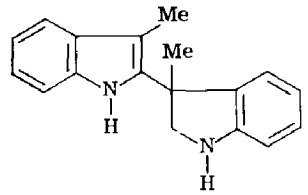


(28)

o-nitrophenylacetaldehyde (**28**) with 2 moles of indole, followed by the reduction of the nitro group.

3. *Skatole Dimer*

Again based on the failure of 2-methylindole to form a dimer, Schmitz-DuMont proposed structure (**29**) for skatole dimer. Structure (**30**) was, however, shown to be the correct one independently in three



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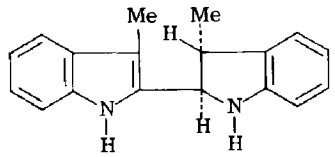
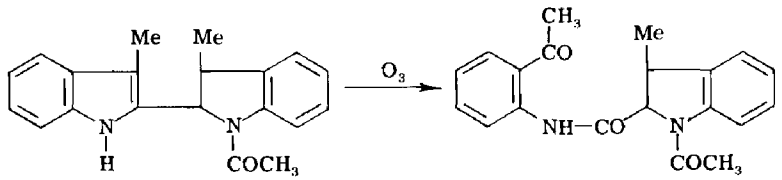


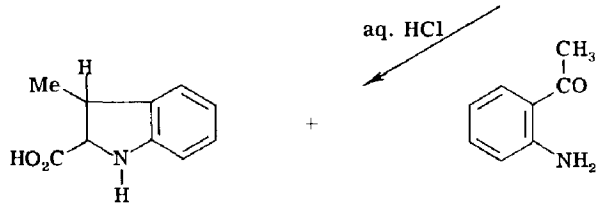
(30)

laboratories.[45,51,52] The most direct proof was provided by Berti *et al.*[51] who ozonized acetyldiskatole (**31**) to compound (**32**), which was hydrolyzed to *o*-aminoacetophenone (**33**) and the amino acid (**34**). This amino acid was then dehydrogenated to skatole-2-carboxylic acid (**35**) under most unusual and mild conditions, in acetone at room temperature. The Italian workers also dehydrogenated diskatole to diskatyl (**36**) with chloranil; the diskatyl was then

[51] G. Berti, A. De Settimo, and D. Segnini, *Tetrahedron Letters* No. 26, 13 (1960).
[52] R. L. Hinman and E. R. Shull, *J. Org. Chem.* **26**, 2339 (1961).



(31) (32)



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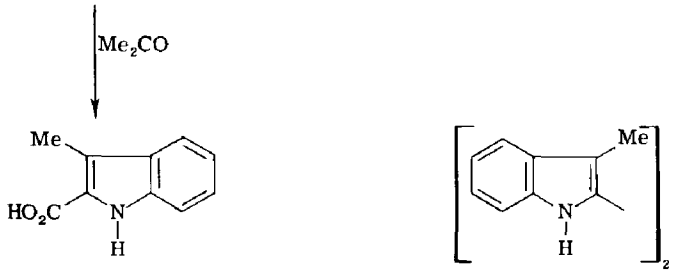

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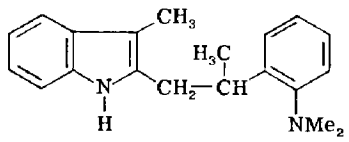

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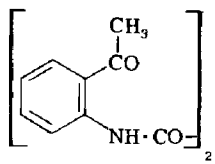
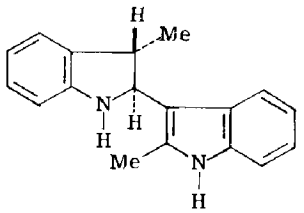


(37)

ozonized to the oxalyl derivative of *o*-aminoacetophenone (**37**). Other proofs of structure involve oxidation of the Emde base derived from diskatole (**38**), to methylsuccinic acid[45] and an analysis of the NMR spectrum.[52]

4. *The Mixed 2-Methylindole–Skatole Dimer*

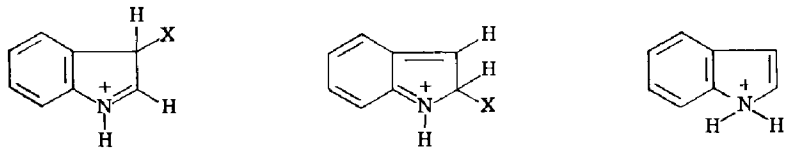
The structure (**39**) proposed for this compound[53] by analogy with indole and skatole dimers was confirmed by an analysis of the NMR spectrum.[52]



(39)

C. Discussion of the Mechanism of Polymerization of Indoles

It is well known that electrophilic attack of the indole nucleus occurs much more readily in position 3 than in position 2. An inspection of the cations produced by electrophilic addition at carbon provides what is probably the main reason for this. It is obvious that cation (**40**), with an intact benzene ring, will be much stabler than cation (**41**) in which the ring is involved in an *o*-quinonoid mesomeric system. That protonation of the 3-position is also very strongly favored was shown by deuterium exchange studies[54]: it was found that between pH 2.5 and 0.5 only the NH and the hydrogen at position 3 exchange and that the hydrogen at position 2 only begins

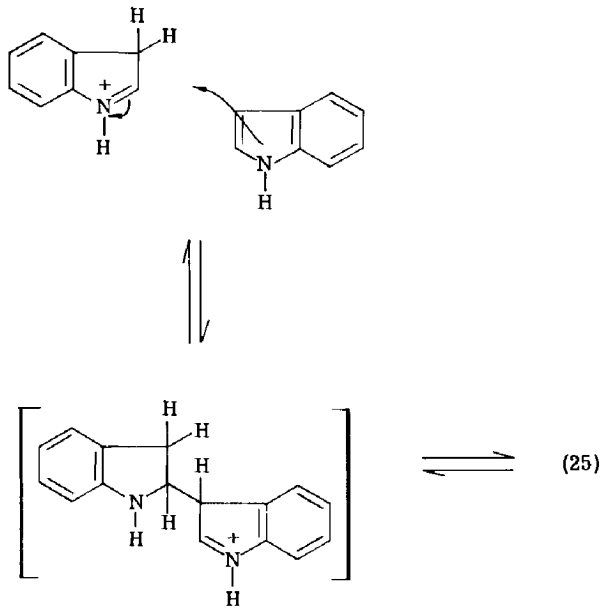


(40) (41) (42)

[53] W. E. Noland and C. F. Hammer, *J. Org. Chem.* **25**, 1525 (1960).
[54] M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan* **13**, 307 (1938).

to exchange at pH values below 0.5. *N*-Protonation (**42**) is the easiest of all, for the NH is deuterated even at pH 7.

Cation (**40**, X = H), since it contains the system $-\overset{+}{N}H{=}CH-$, will be a good electrophilic reagent, and will thus attack the α-position of a neutral indole molecule leading to indole dimer (**25**) by way of the cation (**43**). The reversal of the dimerization then involves



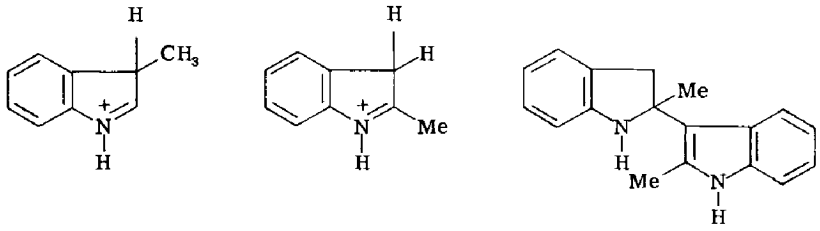
(43)

protonation of the β-carbon of the indole ring in (**25**) leading back to cation (**43**) and then to elimination.

The dimerization of skatole proceeds in an entirely analogous manner, cation (**44**) now being the electrophilic reagent. This is sufficiently reactive to effect substitution at the α-position of a neutral skatole molecule. Attack by the less hindered side of cation (**44**) will be favored, leading to the stereochemistry shown in structure (**30**). The failure of 2-methylindole to dimerize is paralleled by the failure of 2-methylpyrrole dimer to react with a further molecule of 2-methylpyrrole. The main reason is almost certainly again the reduction in the electrophilic character of the immonium carbon by

electron release by the methyl group. That the failure of 2-methylindole to dimerize is not due to a lower susceptibility of position 3 to electrophilic attack is proved by the formation of mixed dimers involving 2-methylindole as one component and indole or skatole, i.e. (**39**), as the other[53] in which the 2-methylindole moiety retains its aromaticity.[52]

The product that 2-methylindole would form if it dimerized, base (**46**), has been synthesized[55] by the $LiAlH_4$ reduction of the 2-methyl-



(44) (45) (46)

indole autoxidation product (**47**). This "dimer" easily dissociates to 2-methylindole on distillation,[45] a behavior also shown by indole dimer.

Dimerization is markedly subject to steric hindrance, thus, whereas 3-*n*-propylindole dimerizes readily, neither 3-isopropyl- nor 3-*tert*-butyl-indole dimerizes. This failure is most probably the result of steric hindrance of approach of the electrophilic reagent to position 2 by the bulky 3-substituent in the unprotonated molecule.[45] On the other hand, models show that approach of a nucleophilic reagent to position 2 of a 3-protonated molecule is quite open, it should, there-

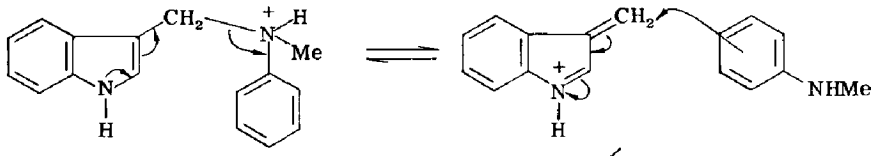
(47) (48)

[55] B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73**, 713 (1951).

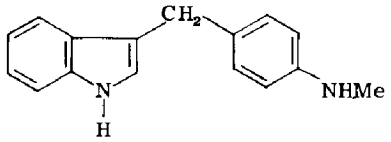
fore, be possible to produce mixed dimers, such as (**48**), of which *neither* component is able to form a homodimer.

Dimerization is also prevented by the presence of a formal positive charge on a β-substituent, thus tryptamine cannot be dimerized.[45]

The formation of the trimer can be rationalized by analogy with the reactions of gramine and its derivatives. Thus, Thesing and Mayer[56] found that methylphenylskatylamine (**49**) reacts with

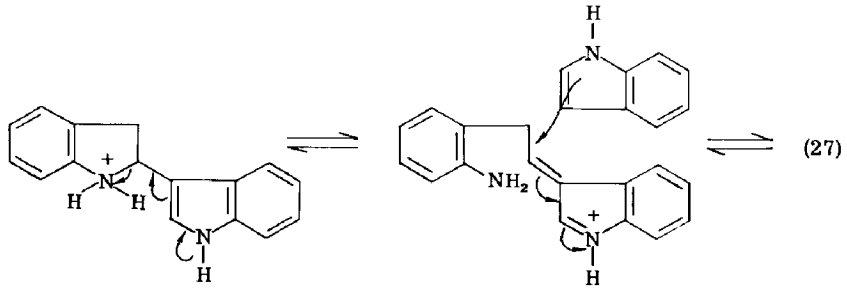


(49) (51)



(50)

methylaniline in the presence of acid to give *N*-methyl-*p*-skatylaniline (**50**). This reaction probably[57] proceeds by initial elimination of methylaniline to give the very reactive species (**51**), which then adds the most readily available nucleophilic reagent.



(53) (52) (27)

The trimerization step can then be seen as formation of the reactive cation (**52**) by ring-opening of protonated indole dimer (**53**), followed by addition of indole as shown to give the trimer (**27**).[53]

The reversal of the trimerization then involves β-protonation of one of the indole nuclei of the trimer, followed by elimination of indole to give cation (**52**).

[56] J. Thesing and H. Mayer, *Chem. Ber.* **87**, 1084 (1954).
[57] J. D. Albright and H. R. Snyder, *J. Am. Chem. Soc.* **81**, 2239 (1959).

1,3-Oxazine Derivatives

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I. Introduction

The last decade has brought a considerable increase of the number of papers concerned with 1,3-oxazine derivatives. This is due partly to the fact that these compounds show interesting reactivity. Hence, it was suggested recently that 1,3-oxazine derivatives (including benz-1,3-oxazine derivatives) should be used as chemotherapeutic agents.[1-9]

[1] T. Urbański, *Nature* **168**, 562 (1951).

[2] T. Urbański, B. Serafinowa, S. Malinowski, S. Ślopek, I. Kamieńska, J. Venulet, and K. Jakimowska, *Gruźlica* (*Tuberculosis*) **20**, 157 (1952).

[3] T. Urbański, S. Malinowski, B. Serafinowa, B. Chechelska, H. Dąbrowska, J. Falęcki, D. Gürne, L. Halski, S. Ślopek, I. Kamieńska, J. Venulet, K. Jakimowska, and A. Urbańska, *Gruźlica* (*Tuberculosis*) **22**, 681 (1954).

[4] T. Urbański, *Chem. Tech.* (*Berlin*) **6**, 442 (1954).

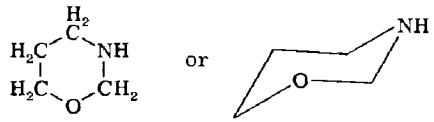
[5] T. Urbański, D. Gürne, Z. Eckstein, and S. Ślopek, *Bull. acad. polon. sci., Classe III* **3**, 397 (1955).

Karrer[10] thought that the dihydro-1,3-oxazine skeleton can possibly be formed in proteins during their transformation to polypeptides. Fodor[11,12] and Fieser[13] explained the stereospecific migration of acyl groups from N to O and vice versa in tropine alkaloids by an intermediate formation of a 1,3-oxazine ring.

II. Nomenclature

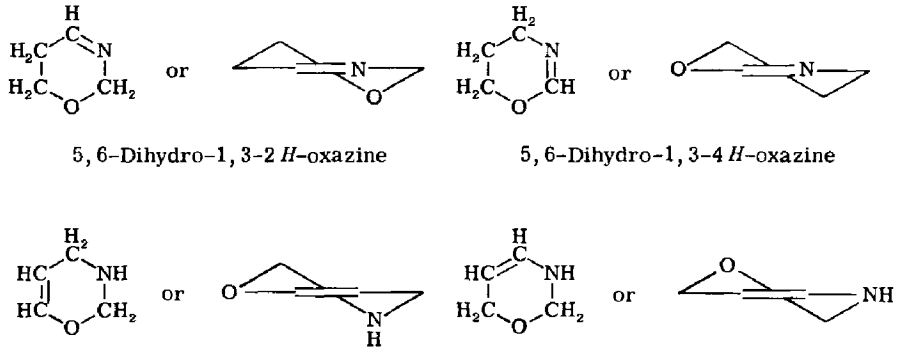
1,3-Oxazine, metoxazine (or mazoxin), consists of a ring of four carbon atoms, one oxygen, and one nitrogen atom; the two hetero atoms are in the 1,3-positions or *"meta,"*

They can be further classified according to the degree of saturation and the position of double bonds. The fully saturated ring is tetrahydro-1,3-oxazine:



The compounds with one double bond are dihydro-1,3-oxazines, and the structures shown in Fig. 1 are possible. The conformations of dihydro-1,3-oxazine rings are based on analogy with cyclohexene and also on the conformational analysis of several benzo-1,3-oxazine derivatives.

[6] T. Urbański, Cz. Radzikowski, Z. Ledóchowski, and W. Czarnocki, *Nature* **178**, 1351 (1956).
[7] T. Urbański, *Ceskoslov. farm.* **6**, 29 (1957).
[8] T. Urbański, Cz. Bełżecki, B. Chechelska, B. Chylińska, H. Dąbrowska, J. Falęcki, D. Gürne, L. Halski, S. Ślopek, S. Malinowski, B. Serafinowa, J. Żyłowski, I. Kamieńska, J. Venulet, M. Janowiec, K. Jakimowska, A. Urbańska, and A. Kuźniecow, *Gruźlica (Tuberculosis)* **26**, 889 (1958).
[9] T. Urbański, D. Gürne, S. Ślopek, H. Mordarska, and M. Mordarski, *Nature* **187**, 426 (1960).
[10] P. Karrer and R. Widmer, *Helv. Chim. Acta* **8**, 203 (1925).
[11] G. Fodor and K. Nador, *Nature* **169**, 462 (1952).
[12] G. Fodor, *Experientia* **11**, 129 (1955).
[13] A. Nickon and L. F. Fieser, *J. Am. Chem. Soc.* **74**, 5566 (1952).

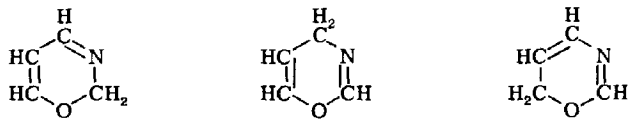


5,6-Dihydro-1,3-2*H*-oxazine — 5,6-Dihydro-1,3-4*H*-oxazine

3,4-Dihydro-1,3-2*H*-oxazine — 2,3-Dihydro-1,3-6*H*-oxazine

FIG. 1. Structures of dihydro-1,3-oxazines.

1,3-Oxazine derivatives with two double bonds can exist in three isomeric forms:



1,3-2-Oxazine	1,3-4-Oxazine	1,3-6-Oxazine
or 1,3-2H-oxazine	or 1,3-4*H*-oxazine	or 1,3-6*H*-oxazine
or 2*H*-1,3-oxazine	or 4*H*-1,3-oxazine	or 6*H*-1,3-oxazine

Of these, only a few representatives of 1,3-4*H*-oxazine are known in the literature.

III. Methods of Preparation of 1,3-Oxazine Derivatives

A general rule can be suggested for one of the principal ways of forming 1,3-oxazine derivatives. They can be formed from 1,3-substituted propane derivatives of general formula:

$$X—CH_2—CH_2—CH_2—Y$$

where

X = NHR and Y = OH, Cl, Br, OCOR′, OCH=CH$_2$, COOR′
X = NHCOR and Y = COOH
X = N_3 and Y = OH
X = NH—C≡N and Y = Br

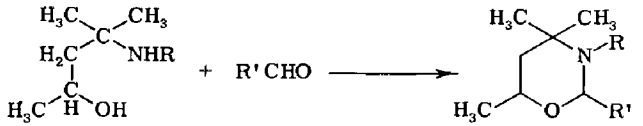
X = N=C=NR and Y = OH
X = OH and Y = OH
X = OH and Y = $OCONH_2$
X = OC(:NH)R and Y = Br.

These compounds can react with various "cyclizing agents," described in the following.

In addition to the compounds just tabulated, a number of less typical methods can also be used to form 1,3-oxazine rings.

A. Tetrahydro-1,3-oxazine Derivatives

The formation of 1,3-oxazine derivatives was reported for the first time by Kohn.[14] It consisted in cyclizing 3-aminopropan-1-ol derivatives with aldehydes to yield tetrahydro-1,3-oxazine derivatives (1).



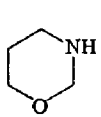
(1)

The reaction was studied by a number of authors and both aldehydes and ketones were used as cyclizing agents.[15-20]

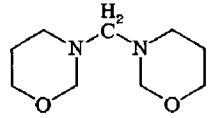
It has been found[15,16,21-27] that those derivatives of 3-aminopropan-1-ol react most readily which contain secondary amino and hydroxyl groups as in the original formation of (1). The reaction can be catalyzed by alkaline reagents, e.g., small amounts of potassium hydroxide.

[14] M. Kohn, *Monatsh. Chem.* **25**, 817 (1904).
[15] C. Mannich and H. Wieder, *Ber. deut. chem. Ges.* **65**, 385 (1932).
[16] C. Mannich and K. Roth, *Arch. Pharm.* **274**, 527 (1936).
[17] A. I. Kiprianov and B. A. Rashkovan, *Zhur. Obshcheĭ Khim.* **7**, 1026 (1937); *Chem. Abstr.* **31**, 5356 (1937).
[18] E. M. Hancock, E. M. Hardy, D. Heyl, M. E. Wright, and A. C. Cope, *J. Am. Chem. Soc.* **66**, 1747 (1944).
[19] G. A. R. Kon and J. J. Roberts, *J. Chem. Soc.* p. 978 (1950).
[20] E. D. Bergmann and A. Kaluszyner, *Rec. trav. chim.* **78**, 315 (1959).
[21] M. Kohn, *Monatsh. Chem.* **25**, 850 (1904).
[22] M. Kohn, *Monatsh. Chem.* **26**, 939 (1905).
[23] M. Kohn, *Monatsh. Chem.* **28**, 423 (1907).
[24] K. Hess and Cl. Uibrig, *Ber. deut. chem. Ges.* **48**, 1974 (1915).
[25] M. Kohn, *Ber. deut. chem. Ges.* **49**, 250 (1916).
[26] T. Urbański and B. Gac-Chylińska, *Roczniki Chem.* **30**, 185 (1956).
[27] T. Urbański and B. Gac-Chylińska, *Roczniki Chem.* **30**, 195 (1956).

3-Aminopropan-1-ol can react with formaldehyde to form the parent tetrahydro-1,3-oxazine (2) itself. With an excess of formaldehyde, a bicyclic compound (3) is obtained.[20,28]



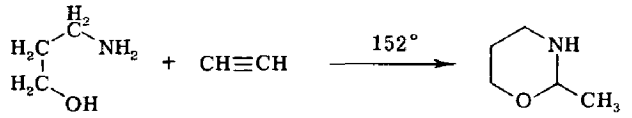
(2)



(3)

It was recently shown[29,30] that the formation of a Schiff's base is the first step of the reaction between 3-aminopropan-1-ol and an aldehyde. The action of acid chlorides, such as tosyl chloride, on the Schiff's base forms the *N*-acyl derivative of tetrahydro-1,3-oxazine.

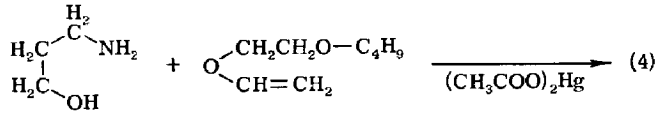
Among various other ways of cyclizing 3-aminopropan-1-ol to a tetrahydro-1,3-oxazine derivative, an interesting reagent is acetylene under pressure[31,32]:



(4)

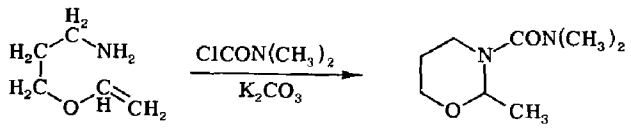
The product (4) is identical with that obtained from 3-aminopropan-1-ol and acetaldehyde.

Vinylbutoxyethyl ether can also be used for the cyclization in presence of mercuric salts[33]:



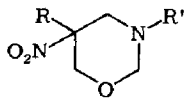
[28] U. S. Patent No. 2911294; *Chem. Abstr.* **54**, 3842 (1960).
[29] S. W. Tsukerman and W. F. Lubomudrov, *Doklady Akad. Nauk S.S.S.R.* **109**, 336 (1956).
[30] W. R. Vaughan and R. S. Klonowski, *J. Org. Chem.* **26**, 145 (1961).
[31] U. S. Patent No. 2778825; *Chem. Abstr.* **51**, 8804 (1957).
[32] W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.* **79**, 2825 (1957).
[33] W. H. Watanabe, *J. Am. Chem. Soc.* **79**, 2833 (1957).

An interesting formation of a tetrahydro-1,3-oxazine derivative (**5**) occurs on reacting the vinyl ether of 3-aminopropan-1-ol with *N*,*N*-dimethylcarbamyl chloride.[31]



(5)

One of the most extensively investigated groups of 1,3-oxazine derivatives is the 5-nitro derivatives of tetrahydro-1,3-oxazine. They were first prepared from 1-nitropropane, aqueous formaldehyde, and ammonia by Hirst *et al.*[34] and independently by Senkus[35,36] from other primary nitroparaffins, formaldehyde, and primary amines. Numerous compounds of the general formula (**6**) were later prepared from primary nitroparaffins.[37-50]



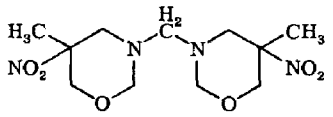
(6)

In formula (**6**), R varies from CH_3 to $C_{15}H_{31}$ when nitroparaffins

[34] E. L. Hirst, J. K. N. Jones, S. Minahan, F. W. Ochynski, A. T. Thomas, and T. Urbański, *J. Chem. Soc.* p. 924 (1947).
[35] U. S. Patent No. 2447822; *Chem. Abstr.* **43**, 1068 (1949).
[36] M. Senkus, *J. Am. Chem. Soc.* **72**, 2967 (1950).
[37] T. Urbański and E. Lipska, *Roczniki Chem.* **26**, 182 (1952).
[38] T. Urbański and D. Gürne, *Roczniki Chem.* **28**, 175 (1954).
[39] D. Gürne and T. Urbański, *Bull. acad. polon. sci., Classe III* **3**, 175 (1955).
[40] T. Urbański and H. Piotrowska, *Roczniki Chem.* **29**, 379 (1955).
[41] T. Urbański and J. Kolesińska, *Roczniki Chem.* **29**, 392 (1955).
[42] T. Urbański, Z. Eckstein, and W. Sobótka, *Roczniki Chem.* **29**, 399 (1955).
[43] D. Gürne and T. Urbański, *Bull. acad. polon. sci., Classe III* **4**, 221 (1956).
[44] T. Urbański, H. Dąbrowska, H. Piotrowska, and B. Lesiowska, *Roczniki Chem.* **31**, 687 (1957).
[45] D. Gürne and T. Urbański, *Roczniki Chem.* **31**, 855 (1957).
[46] D. Gürne and T. Urbański, *Roczniki Chem.* **31**, 869 (1957).
[47] D. Gürne and T. Urbański, *J. Chem. Soc.* p. 1912 (1959).
[48] D. Gürne and T. Urbański, *Roczniki Chem.* **34**, 881 (1960).
[49] Z. Eckstein, A. Sacha, and T. Urbański, *Tetrahedron* **16**, 30 (1961).
[50] T. Urbański, Cz. Bełżecki, and Z. Eckstein, *Roczniki Chem.* **36**, 879 (1962).

from nitroethane to 1-nitro-*n*-hexadecane were used.[40,41,44,51-53] Commencing with nitromethane gave R = CH_2OH or H.[39,45]

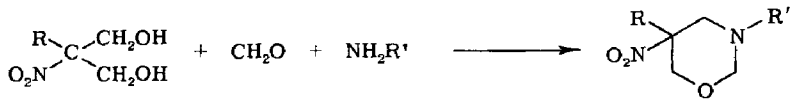
The R′ depends on the amine R′NH_2 used in the reaction. When ammonia was used a bicyclic product (**7**) was formed from nitroethane.[37]



(7)

1-Nitropropane and formaldehyde yielded in presence of ammonia two products of the general structure (**6**): the first with R = C_2H_5, R′ = H and the second with R = C_2H_5, R′ = —CH_2—C(NO_2)(C_2H_5)—CH_2OH (**12**).[34] Higher 1-nitroparaffins, formaldehyde, and ammonia yielded only one product (**6**), R′ = H.

It has been found that the simplest method of preparing 5-nitrotetrahydro-1,3-oxazine derivatives consists in warming 2-alkyl-2-nitropropane-1,3-diol with formaldehyde and ammonia or primary amines:



(6)

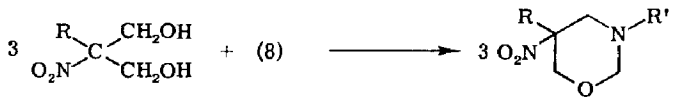
When R = CH_2OH, the reaction was successful only with primary amines, but not with ammonia which yielded only resinous products.

It was recently demonstrated by Eckstein *et al.*[54,55] that the course of the reaction involves the formation of an *s*-triazine derivative (**8**)

[51] T. Urbański, J. Kolesińska, and H. Piotrowska, *Bull. acad. polon. sci., Classe III* **3**, 179 (1955).
[52] Z. Eckstein, P. Gluziński, E. Grochowski, and T. Urbański, *Dissertationes Pharm.*, in press (1963).
[53] Z. Eckstein, P. Gluziński, E. Grochowski, M. Mordarski, and T. Urbański, *Bull. acad. polon. sci., sér. chim.* **10**, 331 (1962).
[54] Z. Eckstein, P. Gluziński, D. Gürne, J. Plenkiewicz, and T. Urbański, *Chem. & Ind. (London)*, p. 1503 (1962).
[55] Z. Eckstein, P. Gluziński, J. Plenkiewicz, and T. Urbański, *Bull. acad. polon. sci., sér. chim.* **10**, 487 (1962).

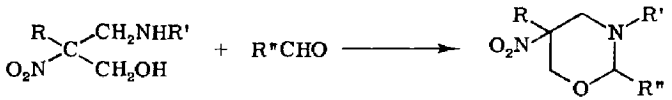
from formaldehyde and the amine. The substance (**8**) acts as a source of formaldehyde and the amine when it reacts with 2-nitropropan-1,3-diol.

(8)



All attempts failed to prepare 5-nitrotetrahydro-1,3-oxazine derivatives from nitromethane, ammonia and formaldehyde,[56] acetaldehyde,[57] or isovaleraldehyde.[42]

The 2-substituted 5-nitrotetrahydro-1,3-oxazine derivatives (**9**) can be obtained by reacting aldehydes with 2-alkyl-2-nitro-3-aminopropan-1-ol (**10**) derivatives. By using various primary amines,

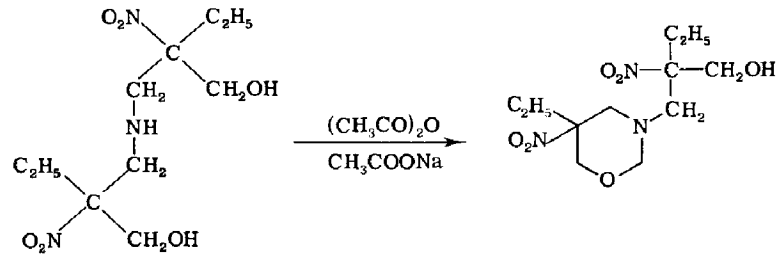


(10) (9)

different 1,3-oxazines substituted in the 3-position have been prepared.[35,36,38,39,44-47,49,58-62]

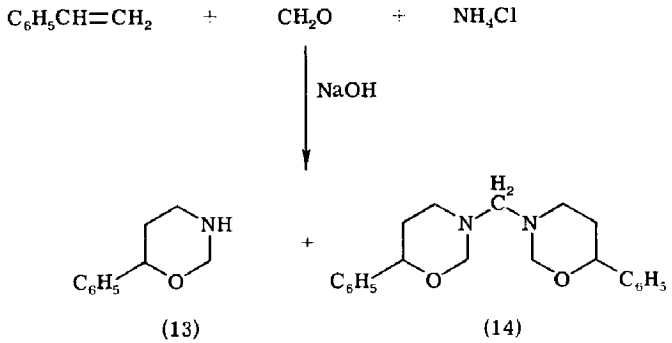
The great tendency of 2-nitro-3-aminopropan-1-ol derivatives to form 1,3-oxazine derivatives (e.g., **12**) was demonstrated[63] when it was attempted to acetylate a derivative of 2-nitro-3-aminopropan-1-ol (**11**).

[56] S. Malinowski and T. Urbański, *Roczniki Chem.* **25**, 185 (1951).
[57] Z. Eckstein and T. Urbański, *Roczniki Chem.* **26**, 571 (1952).
[58] Z. Eckstein, W. Sobótka, and T. Urbański, *Roczniki Chem.* **30**, 133 (1956).
[59] Z. Eckstein and T. Urbański, *Roczniki Chem.* **30**, 1170 (1956).
[60] T. Urbański and H. Piotrowska, *Roczniki Chem.* **31**, 553 (1957).
[61] Z. Eckstein, T. Urbański, and J. Mikulski, *Roczniki Chem.* **33**, 519 (1959).
[62] Z. Eckstein, P. Gluziński, W. Hofman, and T. Urbański, *J. Chem. Soc.* p. 489 (1961).
[63] T. Urbański and B. Szczyciński, *Bull. acad. polon. sci., Classe III* **4**, 225 (1956).



(11) (12)

A new method of preparing tetrahydro-1,3-oxazine derivatives (**13** and **14**) consists in reacting olefins with formaldehyde and ammonium chloride or hydrochlorides of primary amines.[64-71]



(13) (14)

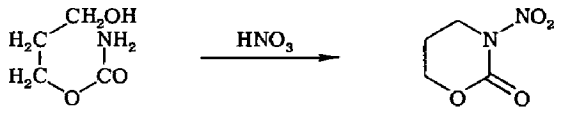
B. Oxo and Thiono Derivatives of Tetrahydro-1,3-oxazine

The 2-oxotetrahydro-1,3-oxazines can be classified as cyclic urethanes. They have been relatively extensively investigated, because of their expected biological activity.

The first preparation of a 2-oxotetrahydro-1,3-oxazine derivative

[64] U. S. Patent No. 2474792; *Chem. Abstr.* **44**, 1131 (1950).
[65] U. S. Patent No. 2647117; *Chem. Abstr.* **48**, 8265 (1954).
[66] U. S. Patent No. 2647118; *Chem. Abstr.* **48**, 7645 (1954).
[67] C. J. Schmiedle and R. C. Mansfield, *J. Am. Chem. Soc.* **78**, 1702 (1956).
[68] S. L. Meisel, J. J. Dickert, and H. D. Hartough, *J. Am. Chem. Soc.* **78**, 4782 (1956).
[69] T. Urbański and B. Szczyciński, *Roczniki Chem.* **30**, 1295 (1956).
[70] U. S. Patent No. 2748140; *Chem. Zentr.* p. 7179 (1957).
[71] U. S. Patent No. 2807613; *Chem. Abstr.* **52**, 8210 (1958).

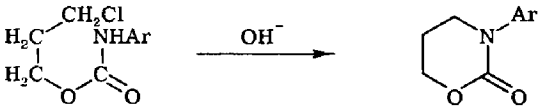
(15) was reported by Franchimont and Lublin.[72] The reaction proceeded from a carbamate:



(15)

Heating dicarbamates with anhydrous zinc chloride also gives 2-oxotetrahydro-1,3-oxazine.[73]

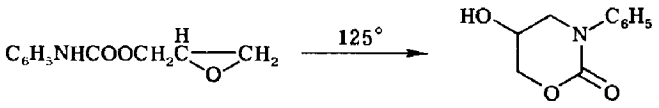
N-Arylcarbamates of γ-halogenopropanols can also be cyclized to *N*-aryl-2-oxotetrahydro-1,3-oxazine derivatives (16)[74–76]:



(16)

A similar reaction of γ-bromopropyl derivatives under the influence of silver nitrate was described by Kohn as early as 1904.[22] The 3-hydroxyketone formed from chloral and acetophenone can react with a chlorocarbamate to yield a pseudourethane which is probably a 4-hydroxy-2-oxotetrahydro-1,3-oxazine.[77]

A number of 5-hydroxy-2-oxotetrahydro-1,3-oxazine derivatives can also be formed from glycide esters of carbamic acid[78]:



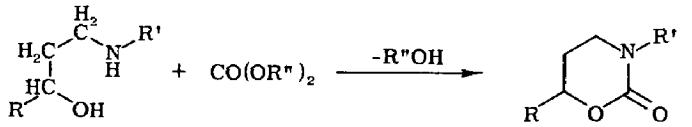
(17)

The same product (17) can be prepared from 3-chloropropan-1,2-diol.[78]

[72] A. P. N. Franchimont and A. Lublin, *Rec. trav. chim.* **21**, 45 (1902).
[73] A. M. Paquin, *Z. Naturforsch.* **1**, 518 (1946).
[74] A. W. Dox and L. Yoder, *J. Am. Chem. Soc.* **45**, 723 (1923).
[75] J. S. Pierce and A. Adams, *J. Am. Chem. Soc.* **45**, 790 (1923).
[76] C. W. Rodenwald and R. Adams, *J. Am. Chem. Soc.* **45**, 3102 (1923).
[77] H. K. Sen and Ch. Barat, *Quart. J. Indian Chem. Soc.* **3**, 405 (1926); *Chem. Abstr.* **21**, 3614 (1927).
[78] Y. Iwakura and Y. Taneda, *J. Org. Chem.* **24**, 1992 (1959).

Some amides can also be converted to 2-oxotetrahydro-1,3-oxazines.[79]

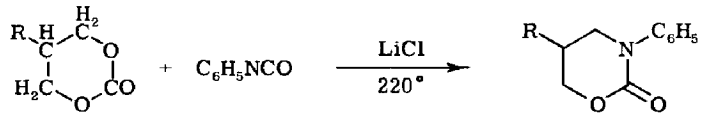
A number of simple reactions are now known which form 2-oxotetrahydro-1,3-oxazine (18). Here, also, 3-aminopropanol and some of its derivatives are frequently used. Cyclizing reagents are: carbonic acid esters in strongly basic medium,[80–87] ethyl chloropropionate,[22] trichloracetic esters,[88,89] or phenyl isocyanate.[87,90] An example of the first of these methods is:



(18)

The reaction is promoted by alcoholates or sodium hydride.

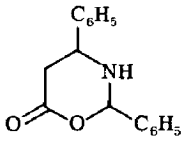
An interesting method of forming 2-oxo-3-phenyltetrahydro-1,3-oxazine (19) and its derivatives was recently given by Gulbins *et al.*[91] It consists of heating a 2-oxo-1,3-dioxane with phenyl isocyanate:



(19)

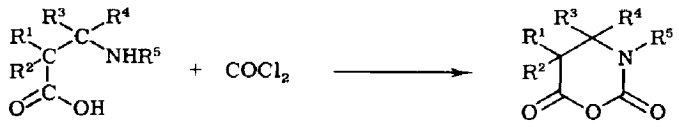
[79] R. Wm. Humphreys, J. Pryde, and E. T. Waters, *J. Chem. Soc.* p. 1298 (1931).
[80] R. Delaby, R. Damiens, and G. d'Huyteza, *Compt. rend. acad. sci.* **239**, 674 (1954).
[81] K. Hayes, *J. Am. Chem. Soc.* **77**, 2333 (1955).
[82] U. S. Patent No. 2701246; *Chem. Zentr.* p. 3705 (1956).
[83] U. S. Patent No. 2702292; *Chem. Zentr.* p. 7315 (1956).
[84] U. S. Patent No. 2744897; *Chem. Abstr.* **51**, 448 (1957).
[85] E. Dyer and H. Scott, *J. Am. Chem. Soc.* **79**, 672 (1957).
[86] J. W. Lynn, *J. Org. Chem.* **24**, 711 (1959).
[87] E. Dyer and R. E. Read, *J. Org. Chem.* **24**, 1788 (1959).
[88] G. Y. Lesher and A. R. Surrey, *J. Am. Chem. Soc.* **77**, 636 (1955).
[89] U. S. Patent No. 2843585; *Chem. Zentr.* p. 4606 (1960).
[90] F. B. Dains, E. J. Joss, and F. E. Stubba, *Univ. Kansas Sci. Bull.* **20**, 161 (1931); *Chem. Abstr.* **26**, 2717 (1932).
[91] K. Gulbins, G. Benzing, R. Maysenhölder, and K. Hamann, *Chem. Ber.* **93**, 1975 (1960).

It has also been stated[92] that malonic acid, benzaldehyde, and ammonia can react to form tribenzaldiiminemalonic acid which under the action of hydrochloric acid is transformed into 6-oxo-2,4-diphenyltetrahydro-1,3-oxazine (**20**). This is the only known representative of the 6-oxotetrahydro-1,3-oxazines.



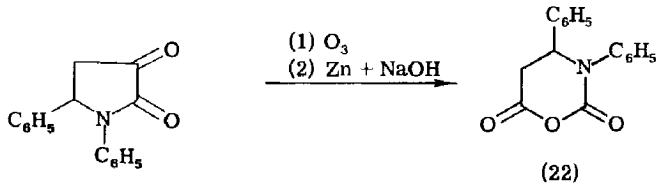
(20)

2,6-Dioxotetrahydro-1,3-oxazine (**21**) can be obtained by reacting phosgene with β-amino acids[93–97]:



(21)

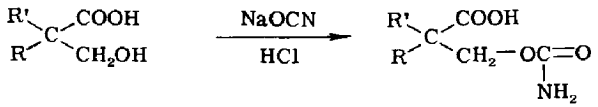
An interesting method for preparing 2,6-dioxo-1,3-oxazine derivatives was described by Wasserman and Koch[98] who stated that the five-membered ring of an α-keto-lactam could be transformed into the 1,3-oxazine (**22**) by ozone followed by reduction with zinc.



(22)

[92] T. Boehm and M. Grohwald, *Arch. Pharm.* **274**, 329 (1936).
[93] U. S. Patent No. 2600596; *Chem. Abstr.* **47**, 7536 (1953).
[94] L. Birkofer and H. Kachel, *Naturwissenschaften* **41**, 576 (1954).
[95] V. Bruckner, T. Vajda, and J. Kovacs, *Acta Chim. Hung.* **6**, 209 (1955).
[96] L. Birkofer and R. Modic, *Ann.* **604**, 56 (1957).
[97] E. Testa, L. Fontanella, and G. F. Cristiani, *Farmaco (Pavia), Ed. sci.* **13**, 437 (1958).
[98] H. H. Wasserman and R. C. Koch, *Chem. & Ind. (London)* p. 428 (1957).

2,4-Dioxotetrahydro-1,3-oxazine derivatives (**24**) can be obtained by reacting β-hydroxy acids with sodium cyanate to form a urethane derivative (**23**) followed by the action of thionyl chloride.[99–101]



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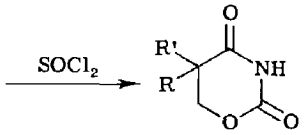
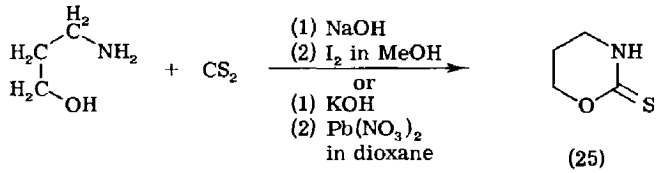


(24)

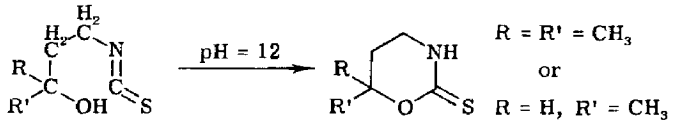
2-Thionotetrahydro-1,3-oxazine derivatives (**25**) can be formed from dithiocarbamates by the action of carbon disulfide on 3-aminopropanol[102,103]:



(25)

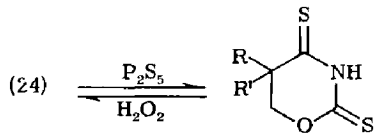
The thiono derivatives of tetrahydro-1,3-oxazine became a subject matter of some interest since Kjaer and Jensen[104] discovered that products of enzymatic hydrolysis of *Malcolma maritima* contain 6-methyl- and 6,6-dimethyl-2-thionotetrahydro-1,3-oxazine (**26**). The authors proved the identity of these compounds with the products of cyclization of 3-hydroxypropyl-isothiocyanate in an alkaline medium.

[99] R. N. Lacey, *J. Chem. Soc.* p. 845 (1954).
[100] E. Testa and L. Fontanella, *Ann.* **625**, 121 (1959).
[101] German Patent (DAS) No. 1074585; *Chem. Zentr.* p. 1661 (1961).
[102] U. S. Patent No. 2326732; *Chem. Abstr.* **38**, 894 (1944).
[103] U. S. Patent No. 2832680; *Chem. Zentr.* p. 15881 (1960).
[104] A. Kjaer and R. B. Jensen, *Acta Chim. Scand.* **12**, 1746 (1958).



(26)

By reacting phosphorous pentasulfide with dioxo derivatives of tetrahydro-1,3-oxazine, the oxygen atoms of both carbonyl groups are replaced by sulfur (**27**)[105]:

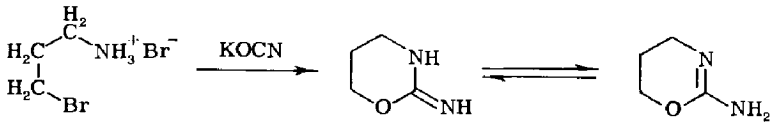


(27)

The reaction is reversible and (**24**) can be recovered by the action of hydrogen peroxide.

C. Iminotetrahydro-1,3-oxazine Derivatives

Gabriel and Lauer first prepared a 2-iminotetrahydro-1,3-oxazine (**28a**) as early as 1890[106] by reacting γ-bromopropylamine hydrobromide and potassium cyanate:



(a) (b)

(28)

By tautomerism the product can also be regarded as a 5,6-dihydro-1,3-4*H*-oxazine derivative (**28b**).

The same compound (**28**) can be prepared from an *N*-guanyl or *N*-nitroguanyl derivative of 3-aminopropanol.[107] Also *N*-(3-hydroxypropyl) derivatives of carbodiimide can be cyclized to yield 2-iminotetrahydro-1,3-oxazine derivative (**29**).[108]

(29)

Other derivatives of 3-aminopropanol and 3-halogenopropylamine can also be used to form 2-iminotetrahydro-1,3-oxazine derivatives.[109-112] In some instances phenylisocyanate can be used as a cyclizing agent.[90]

An interesting method of preparing 2-iminotetrahydro-1,3-oxazine derivatives (**30**) consists in cyclizing *N*-butyl-*N*-(γ-bromopropyl)-cyanamide.[113]

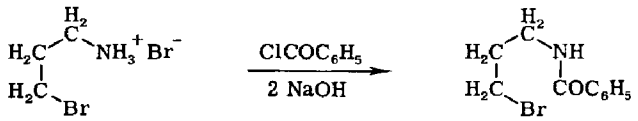
D. 5,6-Dihydro-1,3-4*H*-oxazines

5,6-Dihydro-1,3-4*H*-oxazines (**32**) are among the best known 1,3-oxazines. Their preparation was first described by Gabriel and Elfeldt in 1891.[114] The reaction consisted in benzoylation of γ-bromopropylamine in the presence of sodium hydroxide by an intermediate formation of *N*-benzoyl-γ-bromopropylamine (**31**). The cyclization of the

(30)

benzoyl derivative (**31**) occurred on simple heating, by prolonged keeping of a suspension of (**31**) in water,[114] or by steam distillation.[115-117]

[103] E. Testa, L. Fontanella, G. Cristiani, and G. Gallo, *J. Org. Chem.* **24**, 1928 (1959).
[106] S. Gabriel and W. E. Lauer, *Ber. deut. chem. Ges.* **23**, 87 (1890).
[107] L. Fishbein and J. A. Galleghan, *J. Org. Chem.* **21**, 434 (1956).
[108] E. Schmidt and W. Striewsky, *Ber. deut. chem. Ges.* **47**, 1285 (1914).
[109] D. E. Pearson and M. V. Sigal, *J. Org. Chem.* **15**, 1055 (1950).
[110] P. Chabrier, H. Najer, and R. Giudicelli, *Compt. rend. acad. sci.* **247**, 1350 (1958).
[111] H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France* p. 291 (1959).
[112] H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France* p. 611 (1959).
[113] R. C. Elderfield and M. Green, *J. Org. Chem.* **17**, 442 (1952).
[114] S. Gabriel and P. Elfeldt, *Ber. deut. chem. Ges.* **24**, 3213 (1891).
[115] P. Rehländer, *Ber. deut. chem. Ges.* **27**, 2154 (1894).
[116] A. Luchmann, *Ber. deut. chem. Ges.* **29**, 1420 (1896).
[117] M. Kahan, *Ber. deut. chem. Ges.* **30**, 1318 (1897).



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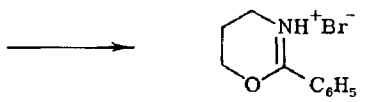
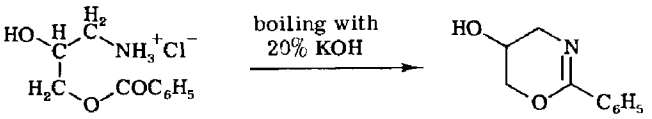


(32)

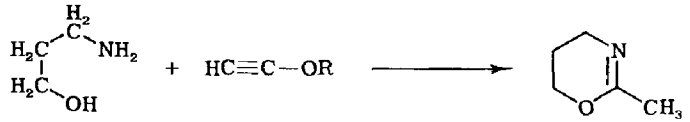
A number of 2-aryl and 2-alkyl derivatives of 5,6-dihydro-1,3-4*H*-oxazine have been prepared in a similar way.[118–120] An analogous reaction consists in thermal cyclization of *N*-(γ-chloropropyl)-*N'*-alkyl and -*N'*-aryl ureas.[110–112,121,122]

5,6-Dihydro-1,3-4*H*-oxazines (33) can be formed from *O*-acyl derivatives of 3-propanolamine even where the formation of smaller rings would also have been possible,[123] e.g.:



(33)

A number of other reagents cyclize 3-propanolamines to 5,6-dihydro-1,3-4*H*-oxazines. These reagents are acetylenic ethers (which act as

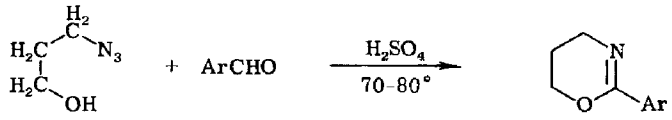


(34)

[118] P. Elfeldt, *Ber. deut. chem. Ges.* **24**, 3218 (1891).
[119] M. Novelli and R. Adams, *J. Am. Chem. Soc.* **59**, 2259 (1937).
[120] M. E. Smith and H. Adkins, *J. Am. Chem. Soc.* **60**, 407 (1938).
[121] H. Najer, P. Chabrier, R. Giudicelli, and J. Sette, *Bull. soc. chim. France* p. 1609 (1959).
[122] H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France* p. 1611 (1959).
[123] S. Gabriel and H. Ohle, *Ber. deut. chem. Ges.* **50**, 819 (1917).

a source of the acyl group) (34),[124–126] esters of unsaturated acids,[127–129] salts of amidines,[130,131] and lactic acid esters.[132] The last probably reacts through an intermediate formation of a lactamide [see also in following the formation of (38)].

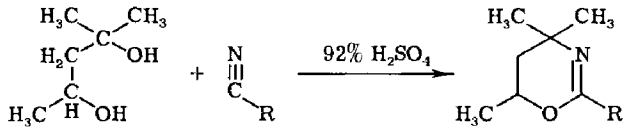
A novel method of forming 2-aryl derivatives of 5,6-dihydro-1,3-4*H*-oxazine (35) consists in reacting 3-azidopropanol with aromatic aldehydes.[133–135]



(35)

Some rather unexpected formations of 5,6-dihydro-1,3-4*H*-oxazines have also been noted, e.g., reaction of γ-bromopropyl iminobenzoate with hydrogen sulfide, which yielded in addition to the main product (thiobenzoate) small amounts of (35):

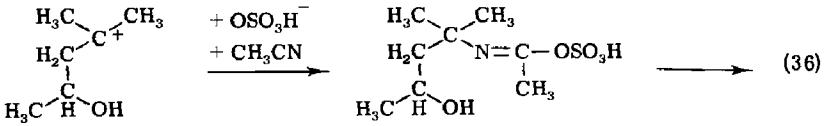
1,3-Propanediol and its derivatives yield 5,6-dihydro-1,3-4*H*-oxazines (36) by reaction with nitriles in the presence of sulfuric



(36)

[124] Dutch Patent No. 81868; *Chem. Zentr.* p. 3980 (1959).
[125] U. S. Patent No. 2813862; *Chem. Zentr.* p. 17309 (1959).
[126] Brit. Patent No. 785373; *Chem. Zentr.* p. 17309 (1959).
[127] I. J. Rinkes, *Rec. trav. chim.* **46**, 268 (1927).
[128] Brit. Patent No. 773011; *Chem. Zentr.* p. 219 (1959).
[129] German Patent No. 953524; *Chem. Zentr.* p. 1143 (1958).
[130] Brit. Patent No. 615006; *Chem. Abstr.* **43**, 7512 (1949).
[131] P. Oxley and W. F. Short, *J. Chem. Soc.* p. 1100 (1950).
[132] W. P. Ratchford, *J. Am. Chem. Soc.* **72**, 3297 (1950).
[133] J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.* **77**, 951 (1955).
[134] J. H. Boyer, F. C. Canter, J. Hamer, and R. K. Putney, *J. Am. Chem. Soc.* **78**, 325 (1956).
[135] Z. Eckstein, K. Majewski, and P. Gluziński, *Roczniki Chem.* **36**, 73 (1962).

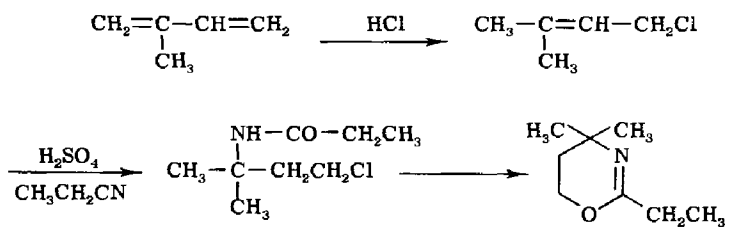
acid.[86,136,137] It was suggested that the reaction occurs via the formation of a carbonium ion (Scheme 1).



(36)

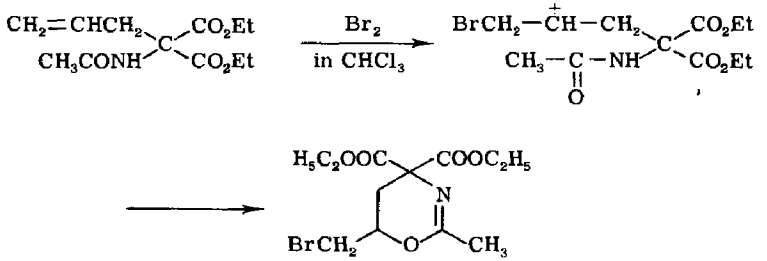
SCHEME 1

Meyers[138] reported a new method of forming 5,6-dihydro-1,3-4*H*-oxazine derivatives (**37**) by reacting chloroolefins with nitriles in an acidic medium.



(37)

Some amides can cyclize to form 5,6-dihydro-1,3-4*H*-oxazine derivatives as already mentioned.[132] A rather complicated reaction of

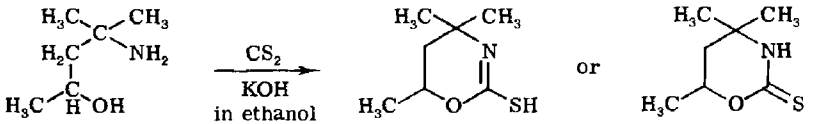


(38)

[136] E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.* **22**, 839 (1957).
[137] A. I. Meyers, *J. Org. Chem.* **25**, 145 (1960).
[138] A. I. Meyers, *J. Org. Chem.* **25**, 1147 (1960).

this type (**38**) is the reaction of ethyl 2-allyl-2-acetamidomalonate with bromine, probably via the formation of an intermediate carbonium ion.

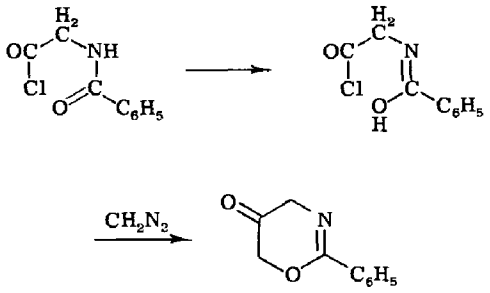
2-Thiol derivatives of 5,6-dihydro-1,3-4*H*-oxazine (e.g., **39**) are formed by reacting carbon disulfide with 3-aminopropanols.[102,139]



(39)

E. Oxo Derivatives of 5,6-Dihydro-1,3-4*H*-oxazine

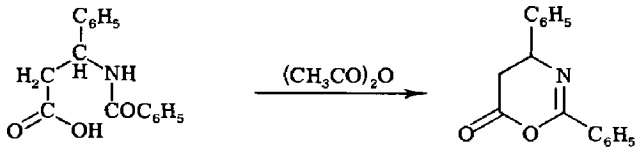
Relatively little is known of this group of compounds. The only compound (**40**) with a keto group in the position 5 was prepared from hippuryl chloride and diazomethane[10]:



(40)

β-Aminoacids are starting materials for the preparation of compounds (**41**) with oxo groups in the 6-position.[140-142] The reaction described by Gosh[140] can serve as an example:

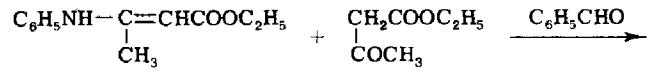
[139] A. A. Rosen, *J. Am. Chem. Soc.* **74**, 2994 (1952).
[140] T. N. Gosh, *J. Indian Chem. Soc.* **11**, 23 (1934); *Chem. Abstr.* **28**, 3736 (1934).
[141] T. N. Gosh and U. P. Basu, *J. Indian Chem. Soc.* **29**, 805 (1952); *Chem. Abstr.* **47**, 12393 (1953).
[142] K. Ivanov, *Doklady Akad. Nauk S.S.S.R.* **109**, 336 (1956).

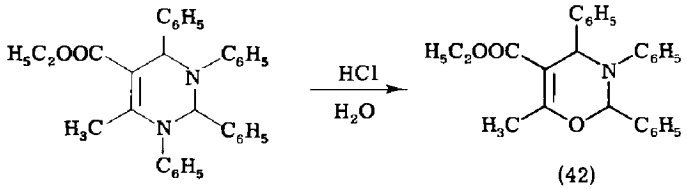


(41)

F. 3,4-Dihydro-1,3-2*H*-oxazines

The only known derivative of this class was prepared from ethyl β-anilinecrotonate, ethyl acetoacetate, and benzaldehyde.[143] In the first instance, a pyrimidine derivative is formed, this is then subjected to partial hydrolysis to form the 3,4-dihydro-1,3-2*H*-oxazine derivative (**42**).

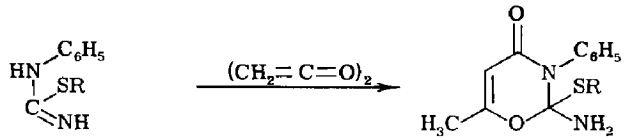




(42)

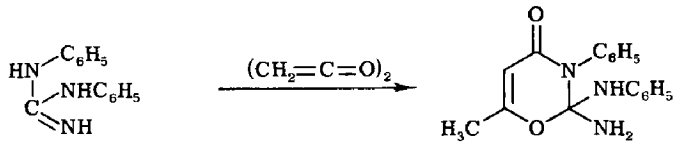
G. Oxo Derivatives of 3,4-Dihydro-1,3-2*H*-oxazine

4-Oxo derivatives (**43** and **44**) can be prepared from isothioureas and guanidines with diketene.[99,144,145]



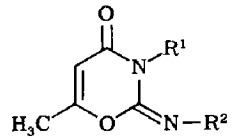
(43)

[143] J. G. Erickson, *J. Am. Chem. Soc.* **67**, 1382 (1945).
[144] R.N. Lacey, *J. Chem. Soc.* p. 839 (1954).
[145] Swiss Patent No. 316158; *Chem. Zentr.* p. 266 (1959).



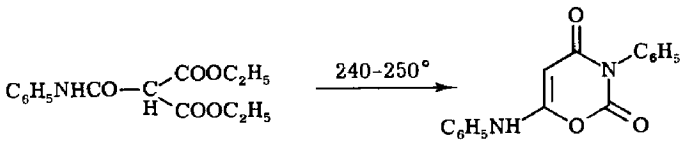
(44)

When an *S*-alkyl-*N,N'*-disubstituted isothiourea reacts with diketene in a boiling solvent,[99,145] 2-imino-4-keto-3,4-dihydro-1,3-2*H*-oxazine derivatives (**45**) are formed. Analogous compounds can be prepared from dialkylcarbodiimides and diketene.[146–148]



(45)

A 2,4-dioxo-3,4-dihydro-1,3-2*H*-oxazine derivative (**46**) was formed[149] by the thermal decomposition of ethyl 2-phenylcarbamoylmalonate:

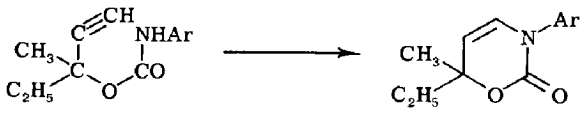


(46)

H. 2,3-Dihydro-1,3-6*H*-oxazines

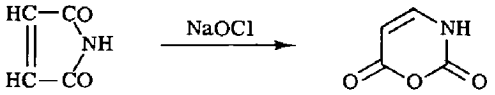
This is the least investigated group of derivatives of 1,3-oxazine. Only oxo derivatives are known. Shapiro *et al.*[150] obtained 2-oxo derivatives (**47**) by cyclizing ethynylalkyl arylcarbamates.

[146] French Patent No. 1085914; *Chem. Zentr.* p. 14071 (1957).
[147] R. N. Lacey and W. R. Ward, *J. Chem. Soc.* p. 2134 (1958).
[148] German Patent No. 960458 (1959).
[149] C. K. Ingold and S. D. Weaver, *J. Chem. Soc.* **125**, 1456 (1924).
[150] S. L. Shapiro, V. Bandurco, and L. Freedman, *J. Org. Chem.* **26**, 3710 (1961).



(47)

Another reaction leading to a 2,6-diketo derivative of 2,3-dihydro-1,3-6*H*-oxazine (**48**) consists in acting with sodium hypochlorite on maleic imide.[127]

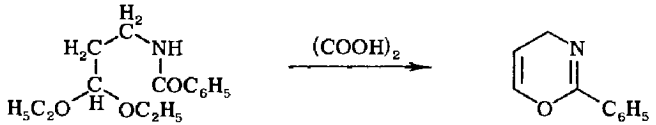


(48)

I. 1,3-4*H*-Oxazines

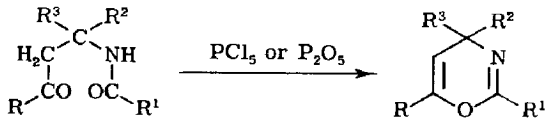
The only known type of 1,3-oxazine containing two double bonds are the 4*H*-isomers.

The first example (**49**) was obtained by Wohl in 1901[151] by reacting an aqueous solution of oxalic acid with the diethyl acetal of γ-benzoylaminopropionaldehyde.



(49)

General methods for the preparation of 1,3-4*H*-oxazines were given by Gabriel[152] and Karrer and Miyamichi.[153] They consist in reacting



(50)

[151] A. Wohl, *Ber. deut. chem. Ges.* **34**, 1914 (1901).
[152] S. Gabriel, *Ann.* **409**, 305 (1915).
[153] P. Karrer and A. Miyamichi, *Helv. Chim. Acta* **9**, 336 (1926).

phosphorous pentachloride and pentoxide, respectively, with β-(*N*-acylamine) derivatives of ketones and carboxylic acid esters.

However, the very existence of 1,3-4*H*-oxazines was questioned by Smith and Adkins.[120] They claimed that no sufficient proof of the structure (**50**) exists. It appears that the problem requires further investigation.

IV. Chemical Properties

A. General

1,3-Oxazines are bases of varying strength and stability. Generally speaking, those which were derived by cyclization using aliphatic aldehydes are more stable than those formed from aromatic aldehydes.[15,16]

1,3-Oxazines can form salts with strong acids. The salts vary with regard to their solubility and stability. Some of the hydrochlorides are hydrolyzed by water.[34,154] Some less common salts are known; e.g., dichromates and ferrocyanates,[106,114,118] chloroplatinates and chloroaurates.[21,22,114,118] Sometimes the picrates can also be used to identify the 1,3-oxazine derivatives.[15,16,21-23,106,108,114,118,135] In some instances a special procedure is required to form the picrates, as the heterocyclic ring can open under the action of picric acid.[154]

1. *Tetrahydro-1,3-oxazines*

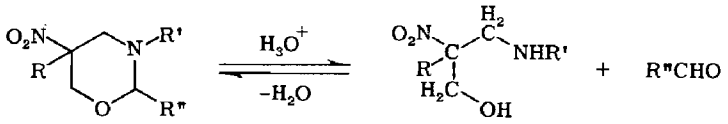
The tetrahydro-1,3-oxazines which contain a free *N*-hydrogen atom can be *N*-acylated[20,30,50,65,68,155] and *N*-nitrosated.[14,21,26,60,80,156] Certain *N*-substituted derivatives of tetrahydro-1,3-oxazines can also react with acetic anhydride to form *N*-acetyl derivatives.[20,67,157] Most tetrahydro-1,3-oxazines add methyl iodide to form quaternary salts.[15,23,34,41,51,58,65,105]

A common feature of tetrahydro-1,3-oxazines is their ability to be hydrolyzed with ring opening. This occurs particularly readily in the presence of dilute mineral acids—preferably methanolic or ethanolic.[26,27,58,158,159] The process can be much speeded up and the yield of

[154] E. Hardegger and H. Ott, *Helv. Chim. Acta* **36**, 1186 (1953).
[155] U. S. Patent No. 2905690; *Chem. Abstr.* **54**, 11058 (1960).
[156] M. Kohn, *Monatsh. Chem.* **25**, 830 (1904).
[157] C. J. Schmiedle and R. C. Mansfield, *J. Am. Chem. Soc.* **77**, 5698 (1955).
[158] R. C. Mansfield and C. J. Schmiedle, *J. Org. Chem.* **21**, 699 (1956).
[159] U. S. Patent No. 2778826; *Chem. Abstr.* **51**, 8809 (1957).

the open-chain compound increased under the influence of ultraviolet light.[26,27,38,108]

Hydrolysis of 5-nitrotetrahydro-1,3-oxazines (**51**) to form 3-amino-2-nitropropanol derivatives (**52**) has been studied most extensively[14,38–41,43,45,46,49,51,58,61]:



(51) (52)

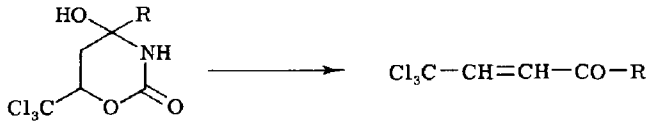
The reaction is reversible and (**52**) can be cyclized with aldehydes under neutral or mildly basic conditions.[49]

The aldehyde R″CHO liberated can be determined quantitatively by means of dinitrophenylhydrazine. In the case of formaldehyde (R″ = H) being split in an alcoholic–acid medium, it has been found that the formation of a dinitrophenylhydrazone is a relatively slow process. This seems to suggest that formaldehyde is originally split off in the form of an acetal which gradually yields formaldehyde under action of dinitrophenylhydrazine.

The opening the hetero ring along the bond O—C (1-2 position) suggests this bond possesses the character of an acetal, or more exactly a hemiacetal. This was suggested by Urbański,[4,160] and later confirmed by his colleagues with the help of infrared spectroscopy.[62,135] Further proof of the hemiacetal character of the O—C bond can be found in the catalytic reduction: ring opening occurs under the action of hydrogen on palladium or on nickel catalyst[64,120,161,162] and reduction with sodium amalgam[163] or with lithium-aluminum hydride.[165]

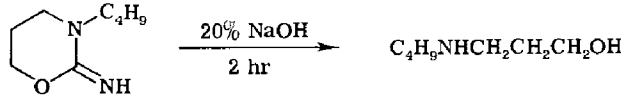
If the acid hydrolysis of 1,3-oxazine derivatives is followed by acting with phenyl-isothiocyanate, thiourea derivatives can be formed.[164]

2-Oxotetrahydro-1,3-oxazine derivatives of type (**53**) can be hydrolyzed to form unsaturated ketones as result of more profound changes in the heterocyclic ring[77]:

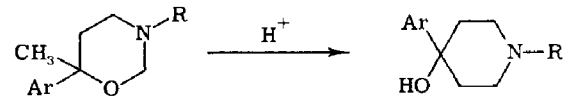


(53)

Ring opening of some derivatives of tetrahydro-1,3-oxazine can also occur when warmed with aqueous sodium hydroxide[113]:



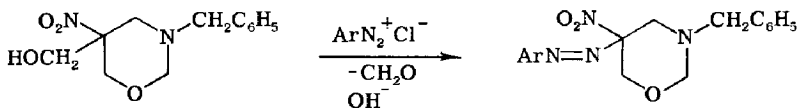
The simple ring opening of tetrahydro-1,3-oxazine derivatives is not the only possible reaction of these heterocyclic compounds catalyzed by mineral acids. An interesting rearrangement of 6-aryl-6-alkyltetrahydro-1,3-oxazines when warmed with concentrated hydrochloric acid was found by Schmiedle and Mansfield[67,157,165]:



This reaction yields derivatives of 1-alkyl-4-aryl-4-piperidinol.[65,158,166–169]

In a basic medium, 5-nitro-5-hydroxymethyltetrahydro-1,3-oxazine derivatives can be coupled with aryl diazonium salts to form arylazo derivatives (**54**) with the elimination of a molecule of formaldehyde.[170]

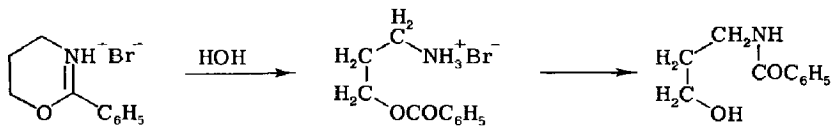
[160] T. Urbański, *Roczniki Chem.* **25**, 257 (1951).
[161] U. S. Patent No. 2550646; *Chem. Abstr.* **45**, 8038 (1951).
[162] A. Pohland, H. R. Sullivan, and R. E. McMahon, *J. Am. Chem. Soc.* **79**, 1442 (1957).
[163] W. Stühmer and W. Heinrich, *Chem. Ber.* **84**, 224 (1951).
[164] U. S. Patent No. 2774790; *Chem. Zentr.* p. 13905 (1958).
[165] C. J. Schmiedle and R. C. Mansfield, *J. Am. Chem. Soc.* **78**, 425 (1956).
[166] U. S. Patent No. 2750285; *Chem. Abstr.* **51**, 4443 (1957).
[167] U. S. Patent No. 2765314; *Chem. Abstr.* **51**, 5844 (1957).
[168] B. G. Boggiano, V. Petrov, and O. Stephenson, *J. Chem. Soc.* p. 1143 (1959).
[169] U. S. Patent No. 2775630; *Chem. Zentr.* p. 9727 (1960).
[170] Z. Eckstein, P. Gluziński, and J. Plenkiewicz, *Bull. acad. polon. sci., sér. chim.* **10**, in press (1963).



(54)

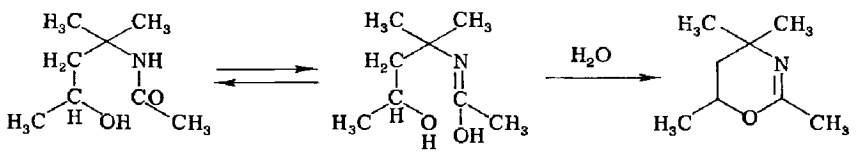
2. *5,6-Dihydro-1,3-4H-oxazines*

Gabriel has demonstrated the instability of 5,6-dihydro-1,3-4*H*-oxazines by reacting the hydrobromide of 2-phenyl-5,6-dihydro-1,3-4*H*-oxazine (**55**) with water.[152] Ring opening occurs with the formation of 3-aminopropylbenzoate which is rearranged into 3-benzamidopropanol.



(55)

A formation of 5,6-dihydro-1,3-4*H*-oxazine derivatives from 3-acetylaminopropanol derivatives has also been described[120,152] (Scheme 2).



SCHEME 2

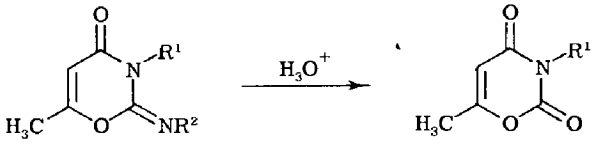
Further examination of the properties of 5,6-dihydro-1,3-4*H*-oxazine derivatives has shown that the ring opening is acid catalyzed.[10,171] Alkaline hydrolysis with 10% NaOH leading to ring opening was also described.[137] The nature of the ring opening is much influenced by the substituents.[132]

3. *3,4-Dihydro-1,3-2H-oxazines*

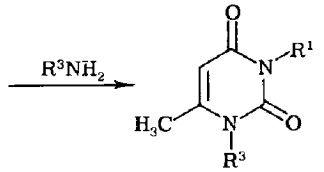
2-Imino derivatives of 4-oxo-3,4-dihydro-1,3-2*H*-oxazines (**56**) are hydrolyzed with dilute hydrochloric acid to the corresponding 2,4-

[171] W. Baker and W. D. Ollis, *J. Chem. Soc.* p. 345 (1949).

dioxo oxazines (**57**).[99] The dioxo (**57**) when warmed with amines is transformed into dioxo-1,2,3,4-tetrahydropyrimidine derivatives (**58**).



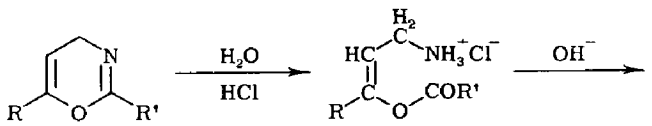
(56) (57)



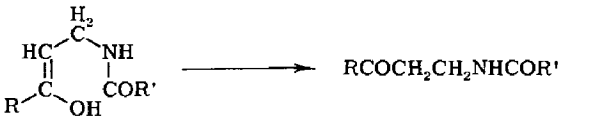
(58)

4. *1,3-4H-Oxazines*

1,3-4*H*-Oxazines (**59**) are also susceptible to hydrolysis by water, particularly in the presence of acids,[152,153] e.g.,



(59)



A noteworthy feature of this sequence of reactions is the O→N migration of the acyl group and the final stabilization as the *N*-acylaminoketone.

B. CHEMICAL STRUCTURE

Although all the syntheses of 1,3-oxazine derivatives and their chemical properties left little doubt as to their chemical constitution,

there was until recently a need for further physicochemical evidence to confirm the structure. This was particularly required as some of the early physicochemical evidence did not fully agree with the structural formulas. Thus, the molecular refraction calculated for 1,3-oxazine derivatives was lower than found experimentally.[20,62] The depression ΔM_D was found to be 0.4–0.9 for 5-nitro derivatives of tetrahydro-1,3-oxazine.

Ultraviolet absorption spectra of tetrahydro-1,3-oxazines do not show any maximum.[26] Only after the introduction of a chromophoric group do bands appear. Thus 5-nitro derivatives show a strong maximum near 270 mμ, which is typical for a nitro group,[40,160,172-175] and another one near 200 mμ which is probably also produced by the nitro group.[40,160,172-175] In the instance of 5-nitro-5-hydroxymethyl derivatives, the absorption is much weakened; this was explained by Urbański[172] in terms of a hydrogen bond between the hydroxyl and the nitro group. Other chromophores, such as C=O, C=NH, C=C, also cause the appearance of absorption maxima in the range 210–265 mμ and near 360 mμ.[24,81,144,147]

Infrared absorption spectra gave more information regarding the structure of 1,3-oxazine derivatives. These studies were mainly concerned with tetrahydro-1,3-oxazine[20,49,62,80,87,105,176] and dihydro-1,3-oxazine derivatives.[62,86,135,137,147,177] According to Eckstein *et al.*[62] a number of bands of frequencies 1150–1050, 955–925, and 855–800 cm^{-1} characterize the hemiacetal bond C—O—C. Lukeš *et al.*[178] expressed the view that a triplet of bands at 1143, 1129, and 1083 cm^{-1} characterized the tetrahydro-1,3-oxazine ring. However, Bergmann and Kaluszyner[20] assigned these bands to the N—C—O system in the tetrahydro-1,3-oxazines.

Other functional groups in tetrahydro-1,3-oxazine derivatives, such as NO_2,[62] CO,[80,87,105] NH (amines),[62] and NH (amides),[80,87,105] give bands whose frequencies are within the generally accepted ranges.

In the case of 5,6-dihydro-1,3-4*H*-oxazine derivatives, the infrared

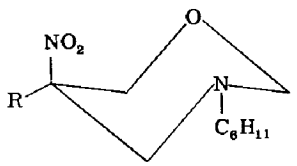
[172] T. Urbański, *Bull. acad. polon. sci., Classe III* **1**, 239 (1953).
[173] T. Urbański, *Bull. Military Tech. Acad. Warsaw* **3**, 31 (1954).
[174] T. Urbański and D. Ciecierska, *Roczniki Chem.* **29**, 11 (1955).
[175] T. Urbański, *Roczniki Chem.* **33**, 635 (1959).
[176] R. Lukeš, J. Kloubek, J. Kovář, and K. Blaha, *Collection Czechoslov. Chem. Communs.* **25**, 483 (1960).
[177] A. I. Meyers, *J. Org. Chem.* **26**, 218 (1961).
[178] R. Lukeš, J. Kloubek, J. Kovář, and K. Blaha, *Collection Czechoslov. Chem. Communs.* **24**, 2433 (1959).

spectra confirmed their structure. A number of papers was also concerned with elucidating the influence of substituents in the 2-position on the C=N stretching frequency which usually has a value near 1650 cm^{-1}.[62,135,137,177] The lowest frequency (1608 cm^{-1}) was recorded[177] when the vinyl group was in the 2-position. Wrong interpretation of some results[86] was corrected by Meyers.[137]

The infrared spectra of 2,4-dioxo and 2-imino-4-oxo-3,4-dihydro-1,3-4*H*-oxazines were also examined[147] and found to confirm their structural formulas. An interesting result here was that the νC=N of the side imino group and the νC=C in the ring have the frequencies 1594–1590 cm^{-1} and 1693–1670 cm^{-1}, respectively.

C. Conformation

Lukeš *et al.*[179] discussed the formation and hydrolysis of tetrahydro-1,3-oxazine derivatives and came to the conclusion that tetrahydro-1,3-oxazine derivatives existed in a chair form similar to that of cyclohexanes. Gürne and Urbański[47] came to the same conclusion on the evidence of measured and calculated dipole moments of 5-nitro-5-alkyl-3-cyclohexyltetrahydro-1,3-oxazines. They found that the 5-nitro group is always axial even when the 5-alkyl group is as small as methyl (**60**).

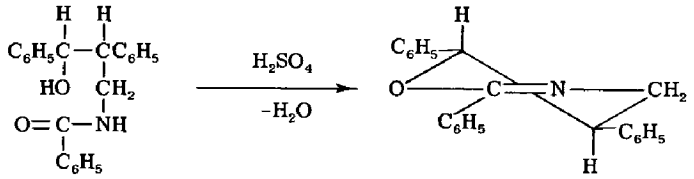


(60)

Drefahl and Hörhold[180] discussed the mechanism of N → O acyl migration in *N*-benzoyl-1,2-diphenyl-3-aminopropanols. The migration does not seem to be possible in the erythro isomer as it would give an intermediate tetrahydro-1,3-oxazine with a bulky phenyl group in axial position. Consequently the erythro isomer is cyclized with inversion to form 2,5,6-triphenyl-5,6-dihydro-1,3-4*H*-oxazine

[179] R. Lukeš, K. Blaha, and J. Kovář, *Chem. Listy* **51**, 927 (1957); *Collection Czechoslov. Chem. Communs.* **23**, 306 (1958).
[180] G. Drefahl and H. H. Hörhold, *Chem. Ber.* **94**, 1641 (1961).

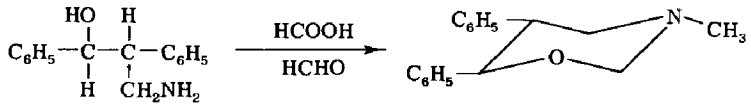
(**61**). Thus a semichair conformation with equatorial phenyl groups is formed.



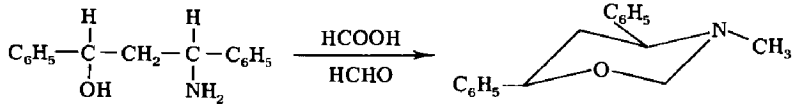
(61)

Similarly in epimeric transformation of *N*-acyl derivatives of 1,3-diphenyl-3-aminopropanol, the formation was accepted[181] of 5,6-dihydro-1,3-4*H*-oxazines with a conformation similar to (**61**).

Stereospecificity was also shown in the reductive aminomethylation[182] of 3-aminopropanol derivatives by the Eschweiler-Clark method. Threo-3-methyl-5,6-diphenyl- (**62**) and erythro-3-methyl-



Threo (62)



Erythro (63)

4,6-diphenyltetrahydro-1,3-oxazine (**63**) were formed as shown, but if starting materials of the opposite configuration were used, then only the corresponding dimethylamino derivatives were formed, and ring closure did not occur.

The formation of various tetrahydro-1,3-oxazine derivatives was used to separate diastereo isomers of 3-amino-1,3-diphenylpropanol.

[181] J. Sicher, M. Pankova, J. Jonas, and M. Svoboda, *Collection Czechoslov. Chem. Communs.* **24**, 2727 (1959).
[182] G. Drefahl and H. H. Hörhold, *Chem. Ber.* **94**, 1657 (1961).

D. Possible Practical Applications

1. *Theoretical Organic Chemistry*

The ability of compounds containing NH and OH (*cis*) groups in the positions 1 and 3 to each other to form a 1,3-oxazine ring can be used to establish the absolute configuration of the corresponding structural fragments in some alkaloids. The method suggested by Hardegger and Ott[154] consisted in forming 1,3-oxazine rings by acting with aldehydes in anhydrous medium. A number of alkaloids were investigated in this manner.[12,17,143,147,154,176,178,179,183-186]

As previously mentioned, N → O acyl migration in derivatives of 3-aminopropanol was proved to occur via the formation of a 1,3-oxazine intermediate.[11,12,13,180,182,187,188]

2. *Biologically Active Compounds*

A number of drugs with a 1,3-oxazine ring have been suggested in connection with chemical work in the field. Lately such interest has increased since a natural product—geissospermine—was found to contain this ring.[189] However, the work in this field is still experimental, based on working hypotheses.

Tetrahydro-1,3-oxazine derivatives were suggested as analgesics and anticonvulsants[190] or analgesics and antipyretics.[88,89,191] Mono- and dioxo-1,3-oxazine derivatives related to cyclic urethanes were suggested as depressants of the nervous system,[105,128] and sedatives.[192] 2-Thiono-4-oxo derivatives were also suggested as anticonvulsants and sleeping drugs.[101] Wider experiments on the chemotherapeutic activity of 1,3-oxazine derivatives were carried out by Urbański *et al.* They were originally concerned with antitubercular activity,[1,2,3,37,38,40] then with other bacteria and viruses,[1,26,27,193] and eventually with oncostatic

[183] K. Alder and H. A. Dortmann, *Chem. Ber.* **86**, 1544 (1953).
[184] O. Kovacs, G. Fodor and I. Weisz, *Helv. Chim. Acta* **37**, 892 (1954).
[185] O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.* **78**, 6193 (1956).
[186] R. Lukeš, J. Kovař and K. Blaha, *Chem. Listy* **50**, 1180 (1956).
[187] N. L. Wendler, *Experientia* **9**, 416 (1953).
[188] K. Koczka and G. Fodor, *Acta Chim. Hung.* **13**, 83 (1957).
[189] M. M. Janot, *Tetrahedron* **14**, 113 (1961).
[190] H. S. Mosher, M. B. Frankel, and M. Gregory, *J. Am. Chem. Soc.* **75**, 5326 (1953).
[191] U. S. Patent No. 2775590; *Chem. Zentr.* p. 7102 (1958).
[192] R. Fusco and E. Testa, *Farmaco (Pavia), Ed. sci.* **12**, 823 (1957); *Chem. Abstr.* **52**, 11853 (1958).

activity.[9,53,69,194] The latter seem to have prospects for practical application.

According to Urbański *et al.*[9] biological activity of 1,3-oxazine derivatives is due to the active CH_2 group in the 2-position. The use of tetrahydro-1,3-oxazines was also suggested against some infections in veterinary service.[83,195] The suggested use of tetrahydro-1,3-oxazines as herbicides[28,61] did not seem to be a success.

Dihydro-1,3-oxazines have been suggested as analgesics,[119] sedatives and spasmolytics,[11] and fungicides.[125,128,135]

Another line of approach to the practical application of 1,3-oxazine derivatives was the suggested use of tetrahydro-1,3-oxazine derivatives as detergents for textile industry,[82] as anticorrosion chemicals,[191,195] and polymers from 2-oxo derivatives as additives to improve the properties of paper and textiles.[132,196,197]

Both tetrahydro- and dihydro-1,3-oxazine derivatives have been suggested as passive components of azo dyes.[198,199]

[193] D. Rożniecka, *Med. Doświadczalna i Mikrobiol.* **3**, 149 (1951); *Chem. Abstr.* **46**, 4675 (1952).
[194] S. Ślopek, T. Urbański, H. Mordarska and M. Mordarski, *Arch. Immunol. Terap. Doświadczalnej* **6**, 503 (1958).
[195] French Patent No. 1094306; *Chem. Zentr.* p. 1143 (1958).
[196] U. S. Patent No. 2806017; *Chem. Abstr.* **52**, 792 (1958).
[197] H. K. Hall and A. K. Schneider, *J. Am. Chem. Soc.* **80**, 6409 (1958).
[198] U. S. Patent No. 2901473; *Chem. Abstr.* **53**, 22968 (1959).
[199] U. S. Patent No. 2873268; *Chem. Abstr.* **54**, 2757 (1960).

The Present State of Selenazole Chemistry

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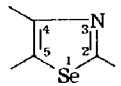
Selenazole is the selenium-containing compound in the series of heterocyclic 5-membered ring azoles with two different hetero atoms, of which the first two members are oxazole and thiazole. The numbering of the ring system is according to the scheme given (1).



(1)

Although there are comprehensive reviews and various specialized publications available covering the field of oxazole and specially thiazole chemistry, this does not apply to the selenazoles. This class of compounds has been treated in a few paragraphs and then only in a few works on organic chemistry.[1] The reason for this is, principally, because in this field so far there has been less work and, correspondingly, a relatively small number of substituted selenazoles are known. Thus the parent compound, selenazole itself, is still unknown, all attempts to synthesize it having failed.

Although the first reported preparations of selenazoles go back to the year 1889, for decades after this no further details were found in

[1] J. D. Loudon, *in* "Chemistry of the Carbon Compounds" (E. H. Rodd, ed.), Vol. IVA, p. 435. Elsevier, Amsterdam, 1957.

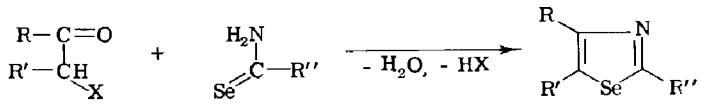
the literature. Only after 1940 was a somewhat more intensive study of the selenazoles begun. In the present chapter, an attempt will be made to review as completely as possible all the known selenazole compounds, together with their methods of preparation and their reactions.

There are probably two grounds for the small number of investigations to be found in the field of selenazole chemistry. One of these is that there is practically only one useful method for preparing selenazoles, in contrast to the many methods available for oxazoles and thiazoles. Corresponding to the Hantzsch thiazole synthesis, this consists of the condensation of α-halogenoketones with selenocarbonamides. In addition, the necessary organoselenium starting materials are rather difficult to synthesize and are sometimes of high toxicity. Further, the greater metallic character of selenium compared to sulfur makes itself very noticeable: as a consequence of this, the selenoamides tend to decompose spontaneously. In particular, their reaction with α-halogenocarbonyl compounds is invariably accompanied by a more or less pronounced precipitation of elementary selenium. This can be confined to reasonable proportions by the careful selection of suitable reaction conditions. Preparative work with this class of compounds is limited because the selenazole ring is relatively unstable and during substitution reactions it can easily be opened, usually with the formation of elementary selenium.

I. Syntheses with Selenazoles

A. Alkyl- and Aryl-Substituted Selenazoles

Attempts to prepare selenazole derivatives were first described by Hofmann,[2] a student of Hantzsch, in connection with investigations in the thiazole series. By reaction of selenobenzamide with α-halogeno compounds corresponding to the general reaction (**2**, $R'' = C_6H_5$), he synthesized a series of 2-phenylselenazoles. In the same way, several



(2)

[2] G. Hofmann, *Ann. Chem. Liebigs.* **250**, 294 (1889).

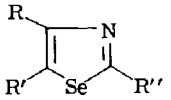
2-alkyl-selenazoles were prepared several decades later from selenoacetamide and selenopropionamide (**2**, $R'' = CH_3$ or C_2H_5).[3,4]

The difficulties encountered in the synthesis of 2-alkyl- and 2-aryl-substituted selenazoles lie principally in the preparation of the corresponding selenoamides. In this respect, a method is worthy of note in which the use of selenoamides is dispensed with. For this, a nitrile, a hydrogen selenide, and an α-halogenoketone are reacted together in the presence of a condensation catalyst.[5] Phosphorus oxychloride, alone or mixed with zinc chloride or phosphorus trichloride, is specially suitable. The yields of the corresponding 2-alkylselenazoles are up to a maximum of 25%.

By this process, 4-methylselenazole (**2**; $R = CH_3$, $R' = R'' = H$) could be obtained by the reaction of hydrocyanic acid and hydrogen selenide with chloroacetone.[5] This is the solitary selenazole unsubstituted in the 2-position that is known. The yield, however, was only 2.5% calculated on the chloroacetone used.

Table I gives details of the alkyl- and aryl-substituted selenazoles

TABLE I
Alkyl- and Aryl-selenazoles



Substituent	Bp/mm (°C)	Mp (°C)	Mp (°C) of picrate	Ref.
2-Methyl	149, 32–34/20	—	170	3,5
4-Methyl	152–153	—	197	5
2,4-Dimethyl	163–164, 54–55/12	—	155	4,5
2,4,5-Trimethyl	176	—	164	5
2-Methyl-4-phenyl	—	63–64	—	3
2-Ethyl-4-methyl	74–76/20	—	—	3
2-Phenyl-4-methyl	282–283/737	—	—	2
2,4-Diphenyl	—	99	—	2
2-Phenyl-4-methyl-5-ethoxycarbonyl	—	123–124	—	2
2-Phenyl-4-methyl-5-carboxy	—	206–207	—	2

[3] Brit. Patent 405,028; *Chem. Zentr.* **105** (II) p. 1250 (1934).

[4] L. G. S. Brooker, G. H. Keyes, and F. L. White, *J. Am. Chem. Soc.* **57**, 2492 (1935).

[5] J. Haginiwa, *Yakugaku Zasshi* **68**, 191 (1948).

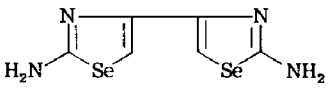
known. In most cases these are oily liquids with a smell which is similar to that of alkyl-pyridines and alkyl-thiazoles. The alkyl-substituted compounds are in part water-soluble. The aryl-substituted selenazoles are water-insoluble. The basicity of these selenazoles is small and their salts are correspondingly easily hydrolyzed in aqueous solution.

B. Amino-selenazoles

1. *From Selenourea*

2-Amino-selenazoles can be prepared by the use of selenourea as the selenoamide component in the Hantzsch synthesis (**2**, R″ = NH_2). The relatively easy accessibility of selenourea has caused more 2-amino-selenazoles to be synthesized than any other type of selenazole derivative. The substituents in the 4- and 5-positions of the selenazole ring depend on the α-halogenoketone component. Thus, from α,β-dichlorodiethylether[2] and chloroacetaldehyde,[6,7] the parent compound 2-amino-selenazole itself is obtained. With other α-halogenoaldehydes, 5-substituted 2-amino-selenazoles[6,7] are produced; with α-halogeno-ketones, 2-amino-selenazoles substituted in the 4- or the 4,5-positions with alkyl or aryl groups have been obtained.[2,7-9] The reaction of halogeno α-keto acids or their esters with selenourea gives the corresponding 2-amino-selenazole-5-carboxylic acids or their esters.[2,9-12] In Table II details are given of 2-amino-selenazoles and their derivatives.

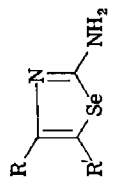
By condensation of selenourea with dibromodiacetyl as the α-halogenoketone, Backer and Bos[8] were able to prepare 2,2′-diamino-4,4′-biselenazole (**3**).



(3)

[6] J. Metzger and P. Bailly, *Compt. rend. acad. sci.* **237**, 906 (1953).
[7] J. Metzger and P. Bailly, *Bull. soc. chim. France* p. 1249 (1955).
[8] H. J. Backer and H. Bos, *Rec. trav. chim.* **62**, 580 (1943).
[9] A. N. Roy and P. C. Guha, *J. Indian Chem. Soc.* **22**, 82 (1945).
[10] E. B. Knott, *J. Chem. Soc.* p. 628 (1945).
[11] U. S. Patent 2,423,709; *Chem. Abstr.* **41**, 6582i (1947); *Chem. Zentr.* **119** (II) p. 253 (1948).
[12] Brit. Patent 593,024; *Chem. Abstr.* **43**, 8401d (1949).

TABLE II
2-Amino-selenazoles

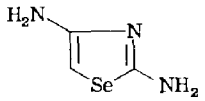


Further substituents	Mp (°C)	Mp of picrate (°C)	Mp (°C)[a]	Ref.
—	121 (121.5)	236	A 210	2, 6, 7
5-Methyl	99	262	HCl 223	6, 7
5-Ethyl	63	239	—	6, 7
4-Methyl	79–80 (78–79)	225 (258)	HCl 189 A 122	2, 7, 8, 9, 27
4-Ethyl	51–52	220 (decomp.)	A 125–125.5	8
4,5-Dimethyl	108–109	257 (decomp.)	HCl 227 (decomp.) A 155–155.5	8
4-t-Butyl	98.5	212–213	HBr 196 A 160.5	8
4-Phenyl	132 (132–133)	198–200 (decomp.)	A 196.5–197.5	2, 7, 8, 9, 14
4-(*p*-Chlorophenyl)	160–160.5 (160–162)	245–248 (decomp.)	A 263–264 (269–270)	8, 14
4-(*m*-Nitrophenyl)	194–195	—	A 306–307	14
4-Phenyl-5-methyl	141–142	—	A 206–207	14
4,5-Diphenyl	189–190	—	A 204–205	14
4-Methyl-5-ethoxycarbonyl	180–181	—	A 216–218	14
4-Methyl-5-carboxy	181–182 (~195)	—	A 220	2, 9
4-Phenyl-5-carboxymethyl	253	—	—	10, 11, 12
4-*p*-Tolyl-5-carboxymethyl	246 (decomp.)	—	—	10
4-Phenyl-5-(α-carboxyethyl)	250 (decomp.)	—	—	10

[a] A = acetyl derivative, HCl = hydrochloride, HBr = hydrobromide.

This forms a dihydrobromide (brown plates) from which the free base is liberated by ammonia. The base crystallizes from nitrobenzene in brown crystals which decompose at 215°C. The picrate of 2,2′-diamino-4,4′-biselenazole decomposes at 254°C.

Davies *et al.*[13] have described the synthesis of 2,4-diamino-selenazole (**4**), by the reaction of selenourea with chloroacetonitrile. The



(4)

hydrochloride does not melt below 250°C; the picrate forms yellow needles of mp 220–225°C. The salts are rather unstable because they slowly deposit selenium even from solutions in hot alcohol. All attempts to liberate the free base from the hydrochloride or to obtain 2,4-dihydroxyselenazole by hydrolysis of the 2,4-diamino compound failed. In each experiment complete decomposition occurred with the deposition of a large amount of selenium.

A variation of the general method for the synthesis of 2-amino-selenazoles is to avoid the use of the free α-halogenocarbonyl compound and in its place react the corresponding ketone and iodine with selenourea.[14] This procedure is also taken from thiazole chemistry. By contrast with thiourea, the reaction with selenourea needs a longer reaction time and the work up of the reaction mixture is somewhat more difficult. Usually an excess of the ketone is used. In the preparation of 2-amino-4-(*m*-nitrophenyl)selenazole, a very high yield, calculated on the amount of iodine used, was obtained. To explain this peculiar result, the oxidative action of the nitro group was invoked. This liberates free iodine from some of the hydrogen iodide eliminated in the condensation reaction, and the free iodine then re-enters into the reaction.

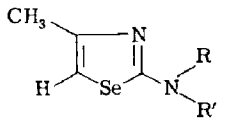
2. *From N-Substituted Selenoureas*

Reaction of *N*-substituted selenoureas with α-halogenocarbonyl compounds yields the corresponding 2-amino-selenazole substituted in

[13] W. Davies, J. A. Maclaren, and L. R. Wilkinson, *J. Chem. Soc.* p. 3491 (1950).
[14] L. C. King and R. J. Hlavacek, *J. Am. Chem. Soc.* **73**, 1864 (1951).

the amino group (**2**, R″ = NHR or NR_2).[15,16] 2-Methylamino-4-methylselenazole was also obtained by the methylation of the potassium salt of 2-acetamido-4-methylselenazole with methyl iodide followed by hydrolysis.[15] The compounds prepared by this method are listed in Table III.

TABLE III
2-ALKYLAMINO- AND 2-ARYLAMINO-SELENAZOLES



Substituents	Mp (°C)	Bp/mm (°C)	Mp of picrate (°C)	Ref.
2-Methylamino-4-methyl	69	126–127/3	213–214 (decomp.)	15
2-Dimethylamino-4-methyl	—	—	176–178 (decomp.)[a]	16
2-Diethylamino-4-methyl	—	125–127/20	165	15, 16
2-Phenylamino-4-methyl	—	—	204–206 (decomp.)	16

[a] Hydrochloride has mp 121–124°C.

3. *Properties*

The 2-amino-selenazoles are crystalline compounds, and sometimes unstable, for example, the parent compound on heating in water undergoes complete decomposition.[2] A few of these selenazoles which are substituted in the amino group are oily liquids. The basic character is more pronounced than in the alkyl- and aryl-selenazoles. The hydrochloride salts are, therefore, not so easily hydrolyzed in aqueous solution. 2-Amino- and 2-methylamino-4-methylselenazole have been considered to exist partly in the tautomeric selenazol-2-one imine form from comparison of their ultraviolet spectrum with that of 2-diethylamino-4-methylselenazole.[15]

The melting point of the ethyl ester[14] of 2-amino-4-methylselenazole-5-carboxylic acid is given as 180–181°C and that of the free acid[9] as 181–182°C. In addition, the melting points of the acetyl derivatives are very close to each other. These facts led King and

[15] J. Haginiwa, *Yakugaku Zasshi* **69**, 566 (1949).
[16] R. A. Zingaro, F. C. Bennett, Jr., and G. W. Hammar, *J. Org. Chem.* **18**, 292 (1953).

Hlavacek[14] to suggest that the ester had been incorrectly described by Roy and Guha[9] as the carboxylic acid. If this is indeed the case, then the corresponding sulfanilamido compound should also be corrected (cf. Table IX and Section II,B,5).

2-Amino-4-aryl-selenazole-5-acetic acids were used by Knott for the preparation of naphtho-1′,2′,4,5-selenazoles.[10,17,18]

C. Hydrazino-selenazoles

$$H_2\underset{1}{N}-\underset{2}{NH}-CSe-\underset{4}{NH_2}$$

(5)

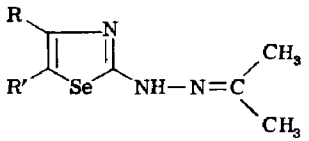
If selenosemicarbazide (**5**) is used as the selenoamide component in the Hantzsch synthesis, the reaction course is now complicated because the molecule is not symmetrical. According as to whether the nitrogen atom in the 1-, 2-, or 4-position of the selenosemicarbazide closes the ring with the α-halogenoketone, three different products can be formed. In order to obtain an authentic hydrazine structure, it is useful to block the N-1 position by the formation of a hydrazone. Condensation of acetone selenosemicarbazone with various α-halogenocarbonyl compounds gave a series of isopropylidene hydrazones of selenazoles [**2**, R″ = NH—N=C(CH$_3$)$_2$].[19,20] These compounds are listed in Table IV. With the exception of the 4,5-diphenyl derivative they are first obtained as the hydrohalide salts, from which the free bases are obtained by reaction with weak alkalies.

Analogously, the corresponding benzylidene hydrazones (**2**, R″ = NH—N=CH—C$_6$H$_5$) could be prepared from the benzaldehyde selenosemicarbazone (cf. Table V).[19,20] These react only as very weak bases, and specially with the compounds which have aryl groups in the selenazole ring, the hydrohalides are very easily hydrolyzed in aqueous solution. The compounds are quite stable to acids and do not show any decomposition even on long keeping. In contrast to the benzylidene hydrazones, the isopropylidene hydrazones of the selenazoles are only stable for a long period in the form of the

[17] Brit. Patent 593,025; *Chem. Abstr.* **44**, 666c (1950).
[18] U. S. Patent 2,476,669; *Chem. Abstr.* **45**, 2027h (1951).
[19] E. Bulka, H.-G. Patzwaldt, F.-K. Peper, and H. Beyer, *Chem. Ber.* **94**, 1127 (1961).
[20] E. Bulka, M. Mörner, and H. Beyer, *Chem. Ber.* **94**, 2763 (1961).

TABLE IV

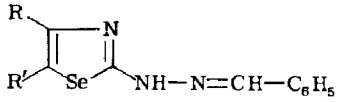
2-Isopropylidenehydrazino-selenazoles[19,20]



Further substituents	Mp (°C)	Mp (°C) of hydrochloride	Mp (°C) of hydrobromide
5-Methyl	156–157 (decomp.)	—	156–157 (decomp.)
4-Methyl	101	171–172 (decomp.)	—
4,5-Dimethyl	138 (decomp.)	173–175 (decomp.)	—
4-Phenyl	108–109	187 (decomp.)	—
4-(*p*-Tolyl)	131	225 (decomp.)	—
4-(*p*-Methoxyphenyl)	125	207	—
4-(*p*-Chlorophenyl)	153	—	223
4-(*p*-Bromophenyl)	154	218 (decomp.)	227 (decomp.)
4,5-Diphenyl	172 (decomp.)	—	—
4-Methyl-5-ethoxycarbonyl	154–155 (decomp.)	169–170 (decomp.)	—
4-Phenyl-5-ethoxycarbonyl	150	194	—

TABLE V

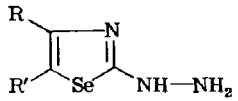
2-Benzylidenehydrazino-selenazoles[19,20]



Further substituents	Mp (°C)	Mp (°C) of hydrochloride	Mp (°C) of hydrobromide	Mp (°C) of acetyl deriv.
5-Methyl	209–210 (decomp.)	—	197 (decomp.)	125
4-Methyl	176	168	—	—
4,5-Dimethyl	192 (decomp.)	202 (decomp.)	—	112
4-Phenyl	188 (decomp.)	214 (decomp.)	—	169–170
4-(*p*-Tolyl)	181	—	206 (decomp.)	189
4-(*p*-Methoxyphenyl)	196 (decomp.)	218 (decomp.)	—	156
4-(*p*-Chlorophenyl)	215	—	240 (decomp.)	—
4-(*p*-Bromophenyl)	220 (decomp.)	—	216 (decomp.)	194
4,5-Diphenyl	230 (decomp.)	—	—	150–151
4-Methyl-5-ethoxycarbonyl	180 (decomp.)	204 (decomp.)	—	114–115
4-Phenyl-5-ethoxycarbonyl	213 (decomp.)	—	—	148

hydrochloride, and they are easily hydrolyzed by means of acids. On this is based the process for the preparation of the free hydrazines[19]: the isopropylidene hydrazones are hydrolyzed with hot, ca. 2 *N* hydrochloric acid. On cooling the filtered reaction mixture, the hydrochlorides of the 2-hydrazino-selenazoles are deposited. With alkali, the free bases can be obtained (cf. Table VI).

TABLE VI
2-HYDRAZINO-SELENAZOLES[19]

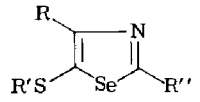


Further substituents	Mp (°C)	Mp (°C) of hydrochloride
5-Methyl	100–102	167–168 (decomp).
4,5-Dimethyl	115	161–162 (decomp.)
4-Phenyl	144–145	166–167 (decomp.)
4-*p*-Tolyl	166	168
4-*p*-Methoxyphenyl	156	170 (decomp).
4-*p*-Bromophenyl	180	187 (decomp.)
4,5-Diphenyl	199 (decomp.)	—
4-Methyl-5-ethoxycarbonyl	187 (decomp.)	198–201 (decomp.)
4-Phenyl-5-ethoxycarbonyl	189 (decomp.)	179

The free selenazole hydrazines are solids, sometimes well crystallized compounds. They show the typical properties of hydrazines. Thus they reduce Fehling's solution on warming and liberate silver, even in the cold, from ammoniacal silver nitrate solution. Further, they react with carbonyl compounds; for example, benzylidene hydrazones are formed with benzaldehyde. These are identical with the hydrazones formed by direct condensation from benzaldehyde selenosemicarbazone and the corresponding α-halogenocarbonyl compound. 2-Hydrazino-4-phenylselenazole has also been reacted with acetophenone. The 2-α-methylbenzylidenehydrazone of 4-phenylselenazole (**2**, R = C_6H_5, R′ = H, R″ = NH—N=CMe·C_6H_5) forms golden yellow plates mp 171°C.[20]

D. Other Selenazole Derivatives

In addition to the selenazole types so far enumerated, a few compounds of diverse structure have been mentioned in the literature.



(6)

In two patents,[21,22] the preparation of thioether-substituted selenazoles of the general formula (**6**) have been described. These are stated to be formed by reaction of halogenoketothioethers with selenoamide components; selenoacetamide, selenobenzamide, and *N*-ethylselenourea are given as examples. The resulting selenazoles were not further characterized. They are stated to be starting materials for the preparation of cyanine dyestuffs which are useful photographically.

4-(2-Pyrryl)selenazole is protected for the same purpose, by another patent.[23] This is stated to be prepared from 2-chloroacetylpyrrole with selenoamides by analogy with the corresponding thiazole. No concrete example of the reaction is given.

Finally, in connection with the investigations on the antineuritic action of homologs and analogs of vitamin B_1, the corresponding seleno compound was also mentioned.[24] However, no details are given on the properties (except mp 203°C) and method of synthesis of this compound.

II. Reactivity of Selenazoles

In a comparison of the chemical properties of thiazoles and the selenazoles thus known, Ochiai[25] concluded that they are mutually very similar. In addition, the evaluation of later experiments shows that only small differences exist between the reactivity of thiazoles and the corresponding selenazoles.

Nevertheless the 2-position of selenazoles appears to be somewhat less reactive than the 2-position of thiazoles toward nucleophilic reagents.[26] However, this conclusion needs further confirmation: as a result of the difficulties in the preparation of suitably substituted

[21] U. S. Patent 2,500,142; *Chem. Abstr.* **44**, 7174g (1950); *Chem. Zentr.* **122** (I) p. 1940 (1951).
[22] Brit. Patent 645,901; *Chem. Abstr.* **45**, 2985i (1951); *Chem. Zentr.* **126**, p. 7359 (1955).
[23] U. S. Patent 2,481,674; *Chem. Abstr.* **44**, 7173b (1950).
[24] F. Schultz, *Z. physiol. Chem.* **265**, 113 (1940).
[25] E. Ochiai, *Yakugaku Zasshi* **69**, 59 (1949).
[26] J. Haginiwa, *Yakugaku Zasshi* **68**, 195 (1948).

selenazoles, it is based on only a few experimental facts. Thus, Haginiwa[26] investigated the reactivity of the 2-position in selenazoles toward nucleophilic substitution using amination as an example. For this purpose he reacted sodamide with 4-methylselenazole at high temperatures in decalin as solvent. The experiments, however, failed and he could only show that ring fission occurred. Because 4-methylselenazole is the only derivative known which is unsubstituted in the 2-position and because it is only available in a very small yield, no further investigations of this type have been undertaken.

Equally, all the attempts of Haginiwa[27] to diazotize 2-amino-4-methylselenazole led to complete decomposition. Later these investigations were taken up by Metzger and Bailly.[7] They tried to prepare selenazoles unsubstituted in the 2-position by means of diazotization and a special Sandmeyer reaction. In spite of variations in the reaction conditions, they were not able to deaminate 2-amino-4-phenylselenazole by this method.

It has also been stated that the 5-position of selenazoles is more reactive toward electrophilic substitution than that of thiazoles.[26] Such reactivity is still further increased by substituents in the 2-position of the selenazole ring, which can have an —E-effect. Simultaneously, however, an increasing tendency toward ring fission was observed by Haginiwa.[27] Reactions of the selenazole ring are thus limited mainly to the 5-position which, specially in the 2-amino- and the 2-hydrazino-selenazoles, is easily substituted by electrophilic reagents. However, all attempts to synthesize selenazole derivatives by the Gattermann and by the Friedel-Crafts methods failed.[15,26]

A. Electrophilic Substitution

1. *Nitration*

Under comparatively mild conditions, already by the action of warm nitric–sulfuric acid, 4-methyl- and 2,4-dimethyl-selenazole were nitrated in the 5-position. 4-Methyl-5-nitroselenazole has mp 45°C,[26] and the 2,4-dimethyl analog has mp 115–120°C (decomp.).[26]

The direct nitration of 2-amino-4-methylselenazole leads to a ring fission.[27] However, if the amino group is previously acetylated, the corresponding 5-nitro compound is formed in good yield: 2-acetamido-4-methyl-5-nitroselenazole, mp 185°C.[27]

[27] J. Haginiwa, *Yakugaku Zasshi* **68**, 197 (1948).

The reaction of nitric acid with 2-diethylamino-4-methylselenazole analogously gave the 5-nitro derivative which formed yellow needles, mp 93°C.[15]

2. *Sulfonation*

The sulfonation of 2,4-dimethylselenazole occurred on heating with fuming sulfuric acid (5% SO_3) at 100°C. The 5-sulfonic acid thus prepared had mp 238°C (decomp.).[26]

3. *Halogenation*

The halogenation of selenazoles goes less smoothly than the nitration and sulfonation. For example the bromination of 2,4-dimethylselenazole with cold bromine first gives an unstable monobromo derivative (mp 168°C). This is transformed easily into a compound of mp 205°C (decomp.) which Haginiwa[26] assumes is the hydrogen bromide salt of 2,4-dimethyl-5-bromoselenazole.

Although direct nitration was not possible, 2-amino-4-methylselenazole can be directly brominated: by treatment with bromine in carbon tetrachloride, the hydrogen bromide salt of 2-amino-4-methyl-5-bromoselenazole, mp 180°C (decomp.) is formed.[27] However, all attempts to obtain the free base from this salt failed and led to complete decomposition. In this bromination, an equivalent quantity of bromine must be used; excess also leads to complete destruction of the molecule. From the decomposition products an oily compound can be detected similar to bromoacetone.[27]

2-Acetamido-4-methylselenazole was also brominated in carbon tetrachloride and gave the 5-bromo derivative, mp 196°C.[27]

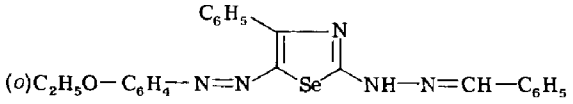
2-Amino-5-bromoselenazole is mentioned in a patent[28] without further details. It is stated to be a starting material for pharmaceutical products. In analogy to the corresponding thiazole compounds, it is stated to be prepared by heating 2-aminoselenazole in aqueous hydrobromic acid under reflux and slow addition of an equivalent amount of bromine.

4. *Azo Coupling*

2-Diethylamino-4-methylselenazole was coupled by Haginiwa[15] with benzene diazonium chloride to yield the corresponding 5-azo compound, which formed orange colored granules, mp 101°C.[15]

[28] U. S. Patent 2,457,078; *Chem. Abstr.* **43**, 3042b (1949).

Bulka *et al.*,[29] during the attempted preparation of selenazole formazans, found that the hydrazones of the selenazoles with unsubstituted 5-positions reacted with diazonium salts to give 5-azo derivatives preferentially. Thus coupling 2-benzylidenehydrazino-4-phenylselenazole with diazotized *o*-phenetidine afforded two compounds that could be separated chromatographically on aluminum oxide. The main product (67%) was 2-benzylidenehydrazino-4-phenyl-5-(*o*-ethoxybenzeneazo)selenazole (**7**), which formed ruby red prisms with a green surface sheen, mp 206°C.[29] The desired formazan formed the minor product (see Section II,B,6).

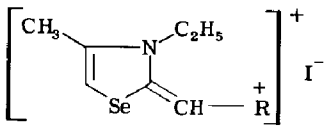


(7)

B. Other Reactions

1. *Quaternary Salts and Cyanine Dyes of Selenazoles*

Because of the basic nitrogen atom, alkyl-selenazoles form quaternary salts. 2,4-Dimethyl-3-ethylselenazolium iodide (mp 157–158°C) was prepared by Brooker *et al.*[4] in 87% yield as colorless crystals by heating of 2,4-dimethylselenazole in excess ethyl iodide for 2 days. By reaction with the corresponding quaternary salts, the following cyanine dyes (**8**) were prepared[4]: 1′3-diethyl-4-methylselenazolo-2′-



(8)

cyanine iodide, mp 259–260°C (decomp.); 1′,3-diethyl-4-methylselenazolo-2-pyridocyanine iodide, mp 232–233°C (decomp.); and 1′,3-diethyl-4-methyl-5′,6′-benzo-selenazolo-2′-cyanine iodide, mp 275–277°C (decomp.).

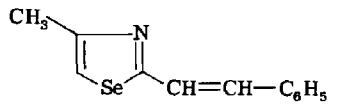
Such quaternary salts are also mentioned in the patent literature as starting materials for the preparation of cyanine dyes which can

[29] E. Bulka, G. Rodekirch, and H. Beyer, *Chem. Ber.* **95**, 658 (1962).

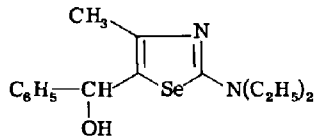
be used photographically. Thus, in a Canadian patent[30] selenazole quaternary salts in general are mentioned. In a U. S. patent,[31] 2,4-dimethyl- and 2-methyl-4-phenylselenazole were mentioned particularly for such quaternary salt formation.

2. *Condensation with Carbonyl Compounds*

A methyl group in the 2-position of the selenazole ring shows the same reactivity as the analogous thiazoles toward carbonyl compounds. By reaction of 2,4-dimethylselenazole with benzaldehyde in the presence of anhydrous zinc chloride catalyst, 4-methyl-2-styrylselenazole (**9**), mp 74–75°C, could be prepared.[26]



(9)



(10)

2-Diethylamino-4-methylselenazole also reacts under the aforementioned conditions with benzaldehyde. The product (prisms, mp 254°C) is obviously (2-diethylamino-4-methylselenazole-5)-phenylcarbinol (**10**).[15] 2-Diethylamino-4-methylselenazole reacts with formaldehyde, but no crystalline reaction product could be isolated.[15]

2-Diethylamino-4-methylselenazole on warming with ethyl orthoformate in the presence of anhydrous zinc chloride gives an intense violet coloration.[15]

3. *Condensation with p-Nitrosodialkylanilines*

Isopropylidene and benzylidene hydrazones of the selenazoles which are unsubstituted in the 5-position react with *p*-nitrosodiethyl- and *p*-nitrosodimethyl-aniline in organic solvents on heating and the addition of acetic acid or pyridine.[32] Thus result crystalline, deeply colored, 2-hydrazono-5-(*p*-dialkylaminophenylimino)selenazoles (correspondingly substituted in the 4-position), details are given in Table VII. The presence of an aromatic residue in the 4-position of the selenazole ring appears to be needed to obtain crystalline compounds.

[30] Can. Patent 441,072; *Chem. Abstr.* **41**, 5039a (1947); *Chem. Zentr.* **119** (I) p. 196 (1948).

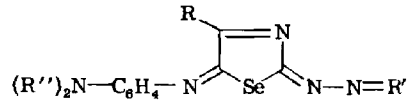
[31] U. S. Patent 2,450,400; *Chem. Abstr.* **43**, 514c (1949).

[32] E. Bulka, H.-G. Patzwaldt, F.-K. Peper, and H. Beyer, *Chem. Ber.* **94**, 2759 (1961).

The dyestuffs in which a 4-alkyl group was present were obtained amorphous—in spite of variation of the reaction conditions, they could not be brought to crystallization. No deposition of selenium which might have resulted from a ring fission could be observed.

TABLE VII

ALKYLIDENE DERIVATIVES OF 5-(*p*-DIALKYLAMINOPHENYLIMINO) SELENAZOL-2-ONE HYDRAZONES

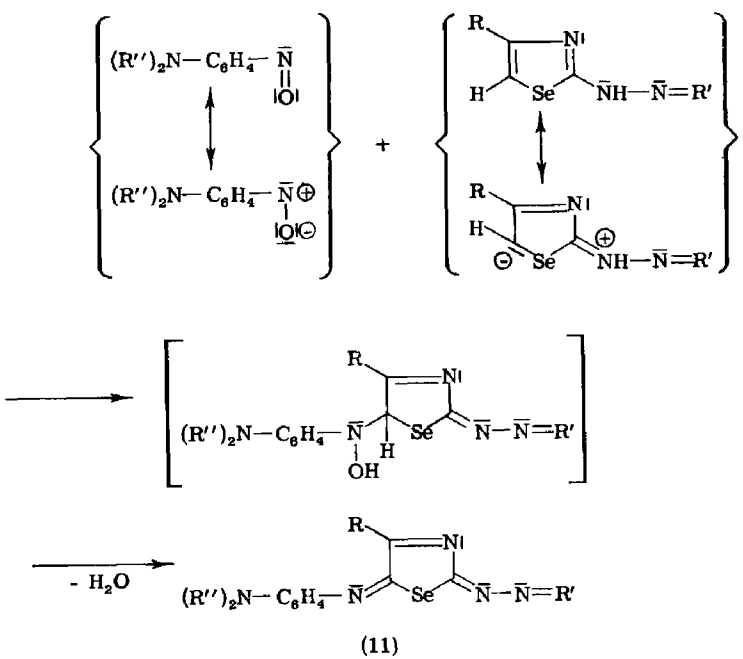


Other substituents	Alkyl of *p*-dialkylamino group	Mp (°C) of isopropylidene derivative	Mp (°C) of benzylidene derivative
4-Phenyl	Ethyl	125	166–167
4-*p*-Bromophenyl	Ethyl	—	163
4-*p*-Tolyl	Ethyl	—	188
4-*p*-Methoxyphenyl	Ethyl	—	121
4-Phenyl	Methyl	154–155	176
4-*p*-Bromophenyl	Methyl	—	207
4-*p*-Tolyl	Methyl	—	185–186
4-*p*-Methoxyphenyl	Methyl	—	165

The reaction mechanism (**11**) is interpreted in that the —E-effect of the hydrazone group in the 2-position of the selenazole ring initially directs negative charge to the 5-position. The electron pair in this position in the mesomeric canonical form then reacts with the nitrogen atom of the polarized nitroso group in the *p*-nitrosodialkylaniline, forming an N—C bond. Simultaneously, a proton is lost from the 5-position and picked up by the negative oxygen atom, and finally elimination of water gives the azomethine.

The dyestuffs show positive solvatochromism on transition to solvents of greater dielectric constant. From this, it is deduced that the compounds are of predominantly nonpolar character.

Substitution of a phenyl residue in the 4-position of the selenazole ring causes only a minor alteration in the position of the absorption maximum. By contrast, the benzylidene compounds are markedly bathochromically shifted compared to the isopropylidene derivatives. Thus the absorption is caused by the whole of the conjugated system, which can be compared to that found in amino derivatives of *N*-



(11)

phenylquinodiimine. In the present case the *para*-quinonoid system of benzene corresponds to the 2- and 5-positions of selenazole. This parallel to the quinonoid dyestuffs of the indoaniline type also extends to the form of the absorption curve, which in almost all details is similar to that of phenol blue derivatives. Further, these compounds are also sensitive toward acids; for example, the deep violet color of the acetone solution is converted to yellow on the addition of mineral acid, but reverts to violet on addition of alkali.

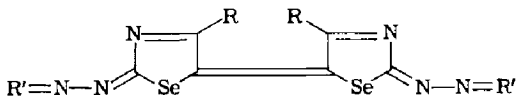
4. *Oxidation to Quinonoid Dyes*

The action of ferric chloride and hydrogen peroxide on isopropylidene and benzylidene derivatives of 2-hydrazinoselenazole yields deeply colored compounds of the 2,2′-dioxo-$\Delta^{3,3'}$-biselenazol-5,5′-inylidene bis-hydrazone type.[20] (Cf. Table VIII.)

The reaction mechanism (**12**) was interpreted as the —E-effect of the hydrazine group in the 2-position of the selenazole ring being the primary cause of the oxidation. An irreversible attachment of two

TABLE VIII

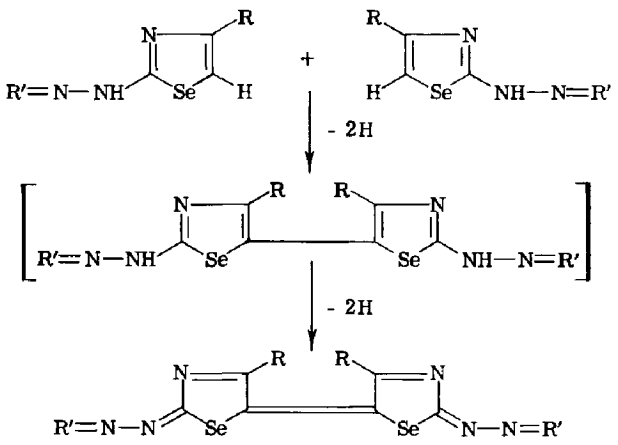
BISALKYLIDENE DERIVATIVES OF 2,2′-DIOXO-$\Delta^{3,3'}$-BISELENAZOL-5,5′-INYLIDENE BIS-HYDRAZONES



Other substituents	Bis-isopropylidene derivative, mp (°C)	Bis-benzylidene derivative, mp (°C)
4,4′-Diphenyl	246	263[a]
4,4′-Di-*p*-chlorophenyl	251	270
4,4′-Di-*p*-bromophenyl	252	291
4,4′-Di-*p*-tolyl	—	292

[a] Bis-α-methylbenzylidene derivative has mp 274°C.

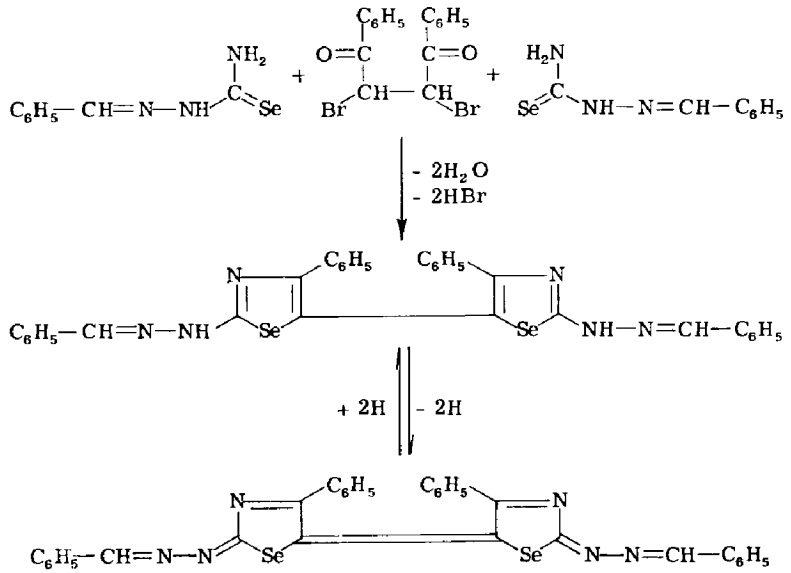
molecules in the 5-position occurs yielding a dihydro product by the simultaneous loss of two hydrogen atoms. This cannot be isolated by direct oxidation, but is at once further dehydrogenated to the quinonoid dye.



(12)

The primary dihydro product can be obtained by reduction of the quinonoid dyestuff. Thus for example 4,4′-diphenyl-2,2′-dioxo-$\Delta^{3,3'}$-biselenazol-5,5′-inylidene bis-benzylidenehydrazone could be reduced to 4,4′-diphenyl-2,2′-benzylidene hydrazino-5,5′-biselenazole (13). This

was identical with the compound obtained by direct condensation of benzaldehyde selenosemicarbazone with 2,3-dibromo-1,4-diphenyl-



(13)

butane-1,4-dione. This synthesis also proves the structure of the dye itself. The dihydro stage is very unstable and is converted by mild oxidation conditions to the dyestuff.

As a result of various side reactions, the yields are relatively low. However, in no case was ring fission found during the oxidations. Specially noteworthy is the ease with which the two methine groups in the 5-position of the 2-hydrazino-selenazoles are coupled together. Reference to models indicates that the quinonoid dyes exist in the *trans* form.

5. *Sulfanilamido-selenazoles*

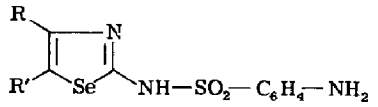
The large importance of the sulfonamides for chemotherapeutics, and specially the high activity of sulfathiazole toward bacterial infections, indicated that sulfonamido derivatives of selenazole should also be investigated. Backer and de Jonge[33] used for this purpose 2-amino-

[33] H. J. Backer and J. de Jonge, *Rec. trav. chim.* **60**, 495 (1941).

4-methyl- and 2-amino-4-phenyl-selenazole in pyridine and reacted it with *N*-acetylsulfanilic acid chloride. From the *N*-acetylsulfanilamides which were thus produced, they obtained by hydrolysis with sodium hydroxide the corresponding 2-sulfanilamido-selenazole. In an analogous way, the other compounds which are given in Table IX were prepared.[9,34,35]

TABLE IX

2-SULFANILAMIDO-SELENAZOLES



Other Substituents	Mp (°C)	Mp (°C) of acetyl derivative	Ref.
—	206	—	34
4-Methyl	222–223, 235, 236–237 (decomp.)	228–229, 255	9, 33, 34, 35
4-Phenyl	209.5–210.5, 231–232	238–239, 244–245	9, 33, 35
4-Methyl-5-carboxy	231–232	238–239	9, 35[a]

[a] See Section I,B,3.

According to investigations of Jensen and Schmith[34] 2-sulfanilamido- and 2-sulfanilamido-4-methyl-selenazole *in vitro* showed the same activity against pneumococci as sulfathiazole. On the other hand, according to Frisk[36] the activity of sulfamethylselenazole is very much less than that of sulfathiazole.

6. *Selenazole-formazans*

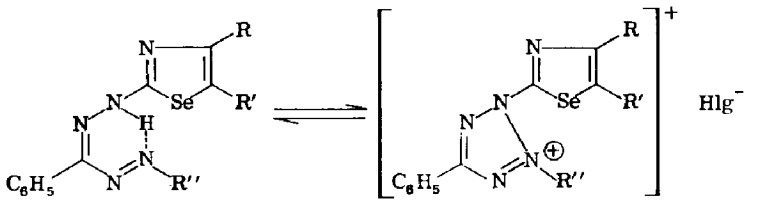
With the synthesis of the benzylidene hydrazones of selenazoles, it was possible to prepare formazans containing a selenazole ring. Of the compounds already described (Section I,C,1), 2-benzylidenehydrazino-4,5-diphenyl- and 2-benzylidenehydrazino-4-methyl-5-carbethoxy-selenazole were used to couple with diazonium salts in order

[34] K. A. Jensen and K. Schmith, *Dansk Tidsskr. Farm.* **15**, 197 (1941); *Chem. Zentr.* **112** (II) p. 2085 (1941).

[35] P. C. Guha and A. N. Roy, *Current Sci. (India)* **12**, 150 (1943); *Chem. Abstr.* **37**, 6653[6] (1943).

[36] A. R. Frisk, *Acta Med. Scand., Suppl.* **142**, 1 (1943); *Chem. Zentr.* **114** (II) p. 638 (1943).

to form formazans.[29] As the diazonium salts derived from aniline, *o*- and *p*-toluidine, *o*- and *p*-anisidine, *o*- and *p*-phenetidine, and *β*-naphthylamine were used. The 1,3-diaryl-5-selenazole-2-formazans (**14**) prepared by this method are well crystallized, deeply colored compounds and possess in part a strong surface sheen. They dissolve in organic solvents with a red-violet to deep blue color. By dehydrogenation the corresponding tetrazolium salts (**15**) were prepared from



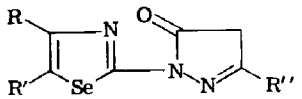
(**14**) (**15**)

the selenazole formazans. It was found that these compounds easily form perbromides.

Whereas reaction of hydrazones disubstituted in the 4,5-position of the selenazole rings with diazotized arylamines only gives formazans, compounds unsubstituted in the 5-position can be attacked there by the diazonium cation. In fact, the azo coupling in this position is decidedly quicker: reaction of 5-benzylidenehydrazino-4-phenylselenazole with diazotized *o*-phenetidine gives 1-(*o*-ethoxyphenyl)-3-phenyl-5-(4-phenylselenazol-2-yl)formazan in only 12% yield. The main product is a 5-azo compound (see Section II,A,4).

7. *Selenazole-pyrazolones*

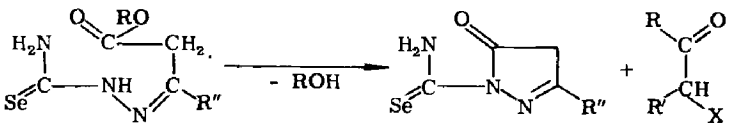
As a further typical reaction of the hydrazine group of the 2-hydrazinoselenazoles (cf. Section I,C,2), pyrazolone formation was investigated. By condensation of the hydrazines with *β*-ketoesters in acetic acid, it was possible to synthesize a series of 1-(selenazol-2-yl)-3-alkylpyrazol-5-ones (**16**).[37]



(**16**)

[37] E. Bulka, W. Dietz, H.-G. Patzwaldt, and H. Beyer, *Chem. Ber.*, in press.

The preparation of the selenazolyl-pyrazolones was then effected by a second method, in which first the pyrazolone ring and afterward the selenazole ring was formed. For this purpose β-ketoester selenosemicarbazones were first converted to the corresponding 1-selenocarbamoyl-3-alkylpyrazol-5-one. These, by condensation with α-halogenocarbonyl compounds according to the Hantzsch synthesis, formed the selenazole ring as a second step (**17**).



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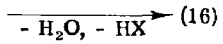

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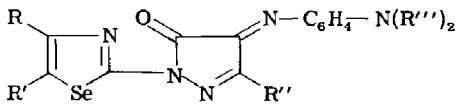
By further reaction of the selenazole-pyrazolones with *p*-nitrosodialkylanilines a number of pyrazolone-azomethines (**18**) was pre-



(18)

pared. These were of interest with reference to a possible use as purple dyestuffs for color photography.

Recent Developments in Isoxazole Chemistry*

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I. Introduction

Isoxazoles are unique in their chemical behavior not only among heterocyclic compounds in general but also among related azoles. This is because isoxazole possesses the typical properties of the aromatic system, which are in fact rather pronounced in these derivatives, together with high lability of the ring under certain conditions, particularly at the nitrogen-oxygen bond. From a purely formal point of view isoxazole can be considered as an analog of pyridine just as

* Translated by A. L. Pumpiansky, Moscow.

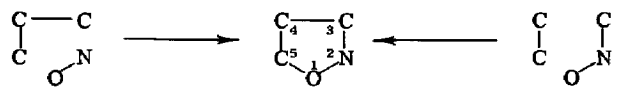
furan is an analog of benzene. Such a formal analogy is to some extent valid, for isoxazole resembles pyridine more than other heterocyclic compounds as far as chemical properties are concerned. It differs from pyridine in undergoing more readily electrophilic substitution reactions and possessing a more labile ring: this relationship thus resembles that between furan and benzene.

Although isoxazole derivatives have been known for more than 80 years, the investigation of their chemistry commenced rather slowly. Earlier studies were mainly devoted to the development of synthetic methods. It is only recently that attention was focused on the investigation of chemical properties and in particular on the peculiarities of the behavior of isoxazole derivatives and the elucidation of their physicochemical characteristics. This enabled new data to be obtained that are of considerable importance.

Previous reviews on the chemistry of isoxazole[1,2] dealt primarily with the synthetic routes and the nucleophilic cleavage of isoxazole derivatives. The first part of the present review is concerned with new investigations in the synthetic field, but the main attention is devoted to a study of the properties of isoxazoles. The review covers studies undertaken during this decade though some earlier works are mentioned when necessary. No complete coverage of the chemistry of partly or fully reduced isoxazoles and their oxo derivatives is attempted, but those aspects of the chemistry of isoxazolines and isoxazolidines that are closely related to the problems under discussion are also mentioned.

II. Synthesis of Isoxazole Derivatives

For the preparation of compounds with an aromatic isoxazole system, two synthetic paths are of high importance: first the condensation to form the 1—5 and the 2—3 bonds of the isoxazole ring (**1**→**2**) and second that to form the 1—5 and 3—4 bonds of this



(1) (2) (3)

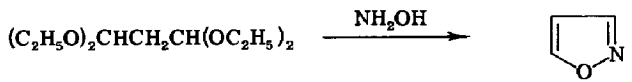
[1] R. P. Barnes, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, Chap. 7. Wiley, New York, 1952.
[2] A. Quilico, *Atti accad. nazl. Lincei, Rend. Classe sci. fis. mat. e nat.* **15**, 357 (1953).

ring (**3**→**2**). No fundamentally new synthetic routes have been suggested recently. We shall, therefore, now review the new variants of the foregoing syntheses and some other studies devoted to their extension.

A. Syntheses of Isoxazoles Which Involve Formation of the 1—5 and 2—3 Bonds of the Isoxazole Ring

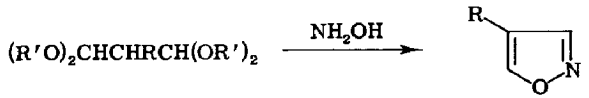
The isoxazole ring is synthesized through the long known and extensively elaborated method of condensing β-diketones or their derivatives with hydroxylamine.

A number of recent papers have described the use of new types of β-diketone derivatives to synthesize isoxazoles. We must first mention 1,1,3,3-tetraalkoxypropanes which are now manufactured on a large scale. Condensation of these derivatives with hydroxylamine has made readily available the parent compound, unsubstituted isoxazole itself (**4**).[3,4] This type of reaction using tetraalkoxypropane



(4)

homologs (**5**→**6**) has made it possible to obtain readily 4-alkylisoxazoles[5] that were formerly practically inaccessible.



(5) (6)

Some polyketones have been used to synthesize diisoxazolyl alkanes, e.g., 1,4-di-(5′-phenyl-3′-isoxazolyl)butane.[6]

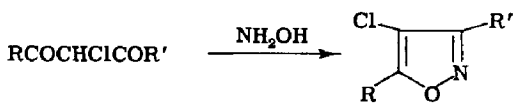
Meso-substituted β-diketones have been found useful to synthesize 3,5-disubstituted isoxazoles with some reactive group in position 4. For example, 3,5-dimethyl-4-(2′,4′-dinitrophenyl)isoxazole (**7**)[7] was

[3] R. Justoni and R. Pessina, *Gazz. chim. ital.* **85**, 34 (1955).
[4] T. V. Protopopova and A. P. Skoldinov, *Zhur. Obshchei Khim.* **27**, 1276 (1957).
[5] T. V. Protopopova, V. T. Klimko, and A. P. Skoldinov, *Khim. Nauka i Prom.* **4**, 805 (1959).
[6] P. Grünanger and E. Fabbri, *Gazz. chim. ital.* **89**, 598 (1959).

prepared in this way as well as 4-chloroisoxazoles (8) substituted in

(7)

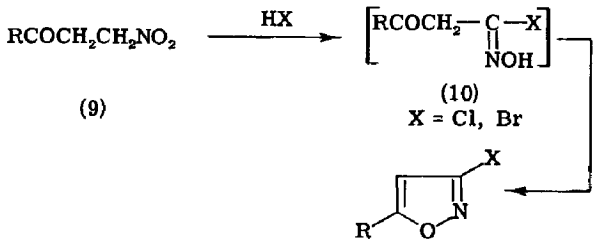
the 3- and 5-positions by alkyl, aryl,[8,9] and other functional groups.[10,11]



(8)

Though not extensively proven, the reaction path leading to only one of the possible isomers is peculiar to this synthesis of 4-chloroisoxazoles. The not infrequent formation of a mixture of two isomeric 3,5-disubstituted isoxazoles, which are difficult to separate, is recognized as one of the chief disadvantages of the use of β-diketones to synthesize isoxazoles.

A particular case of the synthesis of isoxazoles via β-diketone derivatives is the preparation of 3-halogenoisoxazoles (11) from β-nitroketones (9) treated with hydrogen halides.[12,13] This inter-

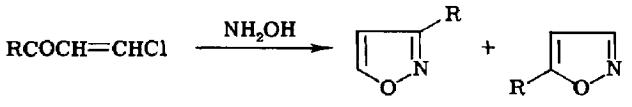


(9) (10) X = Cl, Br (11)

[7] S. S. Joshi and I. R. Gambhir, *J. Am. Chem. Soc.* **78**, 2222 (1956).
[8] N. K. Kochetkov, S. D. Sokolov, N. M. Vagurtova, and E. E. Nifantjev, *Doklady Akad. Nauk SSSR.* **133**, 598 (1960).
[9] S. D. Sokolov and N. K. Kochetkov, *Zhur. Obshchei Khim.* **33**, 1192 (1963).
[10] A. Quilico, R. Fusco, and V. Rosnati, *Gazz. chim. ital.* **76**, 87 (1946).
[11] A. Beelik and W. H. Brown, *Can. J. Chem.* **32**, 288 (1954).
[12] I. Thiele and H. Landers, *Ann.* **369**, 300 (1909).
[13] R. Fusco and S. Rossi, *Chem. & Ind. (London)* p. 1650 (1957).

esting transformation appears to proceed through the intermediate formation of a nonisolated β-ketohydroxamic acid halide (10) and can, therefore, be included in this type of reaction. A considerable number of studies published during the present decade have been concerned with the synthesis of mono- and di-substituted isoxazoles from β-ketoaldehydes and their derivatives.

The well-known reaction of α-alkyl-β-ketoaldehydes and hydroxylamine has been applied to the elucidation of the structure of formylation products of ketones; the conclusions are, however, open to question.[14,15] Some workers attempted to overcome the ambiguity of the reaction of β-ketoaldehydes and hydroxylamine, which results in a mixture of 3- and 5-monosubstituted isoxazoles and thus considerably lowers the preparative value of the method, by using various derivatives of β-ketoaldehydes, especially those of their enolic forms (β-substituted vinylketones) investigated by Kochetkov *et al.* The use of readily available β-chlorovinylketones (12)[16] in the reaction with hydroxylamine represents a rather useful preparative method to synthesize monoalkylisoxazoles but again gives rise to a mixture of 3- (13) and 5-alkylisoxazoles (14).[17,18] This is due to the attack

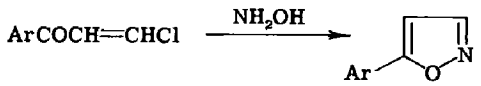


(12) (13) (14)

of hydroxylamine at both the carbonyl and the β-carbon atoms. In some instances this reaction can be directed to favor the formation of one isomer. Thus the reaction of α'-chloroalkyl-β-chlorovinylketones with hydroxylamine, owing to the —I-effect of the chlorine atom, gives chloroalkylisoxazoles with 90–95% content of the 3-substituted isomers.[18,19] It is of interest, though less understandable, that aryl-β-chlorovinylketones (15, with various substituents in the

[14] S. Takagi and H. Yasuda, *Yakugaku Zasshi* **79**, 467 (1959).
[15] H. Yasuda, *Yakugaku Zasshi* **79**, 623 (1959).
[16] N. K. Kochetkov, *Uspekhi Khim.* **24**, 32 (1955); *idem, Chem. Tech. (Berlin)* **7**, 578 (1955).
[17] A. N. Nesmeyanov and N. K. Kochetkov, *Doklady Akad. Nauk SSSR.* **77**, 65 (1951).
[18] N. K. Kochetkov, A. N. Nesmeyanov, and N. A. Semionov, *Izvest. Akad. Nauk SSSR., Otdel. Khim. Nauk* p. 87 (1952).
[19] N. K. Kochetkov and A. Ja. Khorlin, *Zhur. Obshchei Khim.* **28**, 1937 (1958).

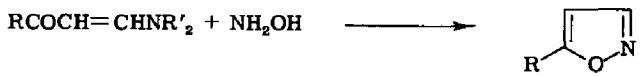
phenyl ring) react with hydroxylamine to give only 5-arylisoxazoles[20] (**16**, Ar = $CH_3C_6H_4$, ClC_6H_4, $O_2NC_6H_4$).



(15) (16)

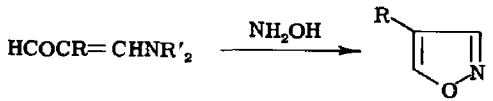
(16, Ar = *p*—$CH_3CH_6H_4$, *p*—ClC_6H_4, *p*—$O_2NC_6H_4$).

When studying the reactivity of β-substituted vinylketones R—CO—CH=CH—X it was found that the electrophilicity of the carbonyl group decreases on passing from chlorovinylketones (X = halogen) to aryloxyvinylketones (X = OAr) and particularly β-dialkylaminovinylketones (X = NR_2). The reaction with hydroxylamine is accompanied by a concurrent nucleophilic substitution of the grouping X for hydroxylamine which increases the percentage of the 5-substituted isomer. The reaction of hydroxylamine with alkyl- and aryldialkylaminovinylketones gives practically exclusively the 5-substituted isoxazole (**17**, R = alkyl, aryl), this method being of preparative value.[21]



(17)

A similar reaction of α-substituted β-dialkylaminoacroleins (**18**), developed by Bredereck *et al.*, proved useful for the synthesis of 4-substituted isoxazoles (**19**).[22]

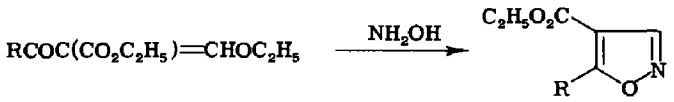


(18) (19)

According to the recent data, α-carboethoxy-β-ethoxyvinylketones (**20**) react with hydroxylamine to form solely 5-substituted isoxazole-

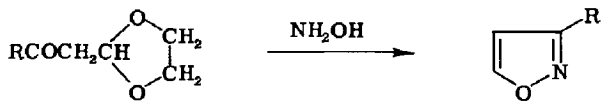
[20] N. K. Kochetkov, E. D. Khomutova, M. Ja. Karpeysky, and A. Ja. Khorlin, *Zhur. Obshchei Khim.* **27**, 452 (1957).
[21] N. K. Kochetkov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, p. 47 (1954).
[22] H. Bredereck, H. Herlinger, and E. Schweizer, *Chem. Ber.* **93**, 1208 (1960).

4-carboxylates (**21**).[23,24] These data contradict the earlier report of Panizzi and Sbrillo-Siena of the formation of 3-substituted isomers in the reaction of β-alkoxyvinylketones.[25]



(20) (21)

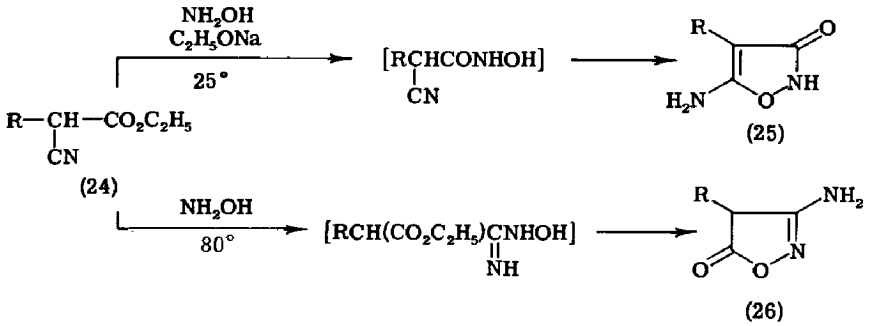
To synthesize 3-substituted isoxazoles directly, Kochetkov and Khomutova have used the reaction of ethyleneacetals of β-ketoaldehydes (readily available from β-chlorovinylketones)[26] with hydroxylamine. Owing to the comparative stability of the dioxolane group, this reaction yields unequivocally the pure 3-substituted isomers (**22** → **23**).[27] The use of noncyclic alkyl β-ketoacetals in this reaction results in a mixture of 3- and 5-substituted isomers.[28]



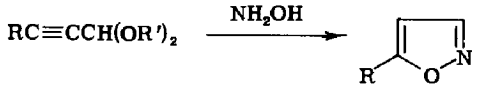
(22) (23)

Several reactions giving rise to hydroxy- and amino-isoxazoles have also been investigated. Thus the reaction of alkoxymethylenecyanoacetates and hydroxylamine leading to 5-amino- or 5-hydroxyisoxazoles proved to be rather useful.[29,30] It is of particular interest that, by changing the reaction conditions, Bauer and Nambury succeeded in obtaining isomeric aminoisoxazolones (**24** → **25** → **26**).[31] It is also possible to prepare isoxazol-3-ones from some β-ketoesters.[32]

[23] R. G. Jones and C. W. Whitehead, *J. Org. Chem.* **20**, 1342 (1955).
[24] H. Yasuda, *Yakugaku Zasshi* **79**, 836 (1959).
[25] L. Panizzi and M. Sbrillo-Siena, *Gazz. chim. ital.* **73**, 335 (1943).
[26] N. K. Kochetkov, E. E. Nifantjev, and A. N. Nesmeyanov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* p. 949 (1957).
[27] N. K. Kochetkov and E. D. Khomutova, *Zhur. Obshchei Khim.* **30**, 954 (1960).
[28] W. Franke and R. Kraft, *Angew. Chem.* **67**, 395 (1955).
[29] H. Kano, Y. Makisumi, and K. Ogata, *Chem. & Pharm. Bull. (Tokyo)* **6**, 105 (1958); *Chem. Abstr.* **53**, 7140 (1959).
[30] A. Dornow and H. Teckenburg, *Chem. Ber.* **93**, 1103 (1960).
[31] L. Bauer and C. N. V. Nambury, *J. Org. Chem.* **26**, 4917 (1961).
[32] A. R. Katritzky and S. Øksne, *Proc. Chem. Soc.* p. 387 (1961).



One of the most important routes to isoxazole and isoxazoline rings involving the formation of the 1—5 and 2—3 bonds involves the condensation of hydroxylamine with α,β-unsaturated carbonyl compounds. This method was previously widely used, but it is now of no preparative value, though it has been recently applied to determine the configuration of oximes.[33,34] The only new modification of this synthesis is the use of the acetals (**27**) of α,β-acetylenic aldehydes for preparation of 5-substituted isoxazoles (**28**).[35,36]



(27) (28)

B. Syntheses of Isoxazoles Involving Formation of the 1—5 and 3—4 Bonds of the Ring

This group of syntheses, of much later origin than that just discussed, is becoming increasingly important both from the practical and the theoretical point of view, as it makes available a large variety of isoxazole derivatives. It includes the formation of isoxazole and Δ^2-isoxazoline rings from unsaturated compounds and hydroxamic acid chlorides or the corresponding nitrile oxides. This group also involves the syntheses of *N*-substituted isoxazolidines from nitrones.

[33] R. Andrisano and G. Pappalardo, *Gazz. chim. ital.* **88**, 113, 174 (1958).
[34] G. Pappalardo, *Gazz. chim. ital.* **89**, 1736 (1959).
[35] A. Quilico, G. Gaudiano, and L. Merlini, *Tetrahedron* **2**, 359 (1958).
[36] A. Ricca and G. Gaudiano, *Atti accad. nazl. Lincei, Rend. Classe sci. fis. mat. e nat.* **26**, 240 (1959).

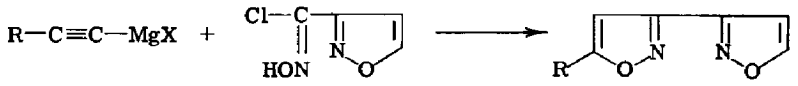
As shown by the Italian school, the formation of isoxazole derivatives by the action of nitric acid or nitrogen oxides on acetylene derivatives and related reactions proceeds through intermediate nitrile oxides and must, therefore, be included with this type of synthesis.

Finally, the condensation of unsaturated compounds with fulminates known as the "fulminic synthesis" represents the simplest case of synthesis from nitrile oxides. Barnes[1] has reviewed in detail the work carried out up to 1953; thus we shall be concerned here only with more recent publications or those of general interest.

The first synthesis of a 3,5-diarylisoxazole from aryl hydroxamic acid chlorides and sodium phenyl acetylides was that effected by Weygand and Bauer in 1927.[37] Beginning in 1946, when Quilico and Speroni showed that acid chlorides of hydroxamic acids on treatment with alkalies readily yielded nitrile oxides,[38] numerous isoxazole and especially Δ^2-isoxazoline derivatives have been prepared.

The experimental conditions for the syntheses starting from acid chlorides of hydroxamic acids and from nitrile oxides are somewhat different. In the former case the other component of the reaction is organometallic, usually an organomagnesium derivative of an acetylene or, less frequently, a sodium enolate of a β-diketone. Nitrile oxides condense directly with unsaturated compounds.

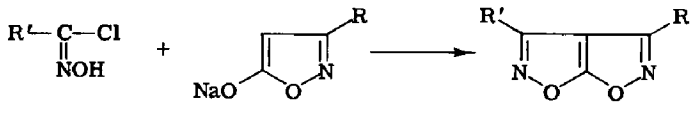
The reaction with hydroxamic acid chlorides has been extensively used recently by Italian chemists to synthesize di- and poly-isoxazolyls, as exemplified by 5-substituted 3,3'-diisoxazolyls (**29**).[39,40]



(29)

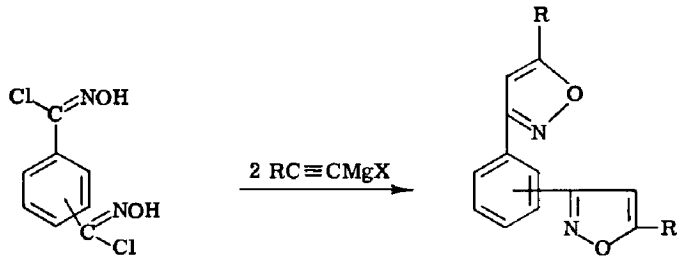
Similarly, there were obtained 3,5'-diisoxazolyl[36] and polyisoxazolyls up to linear octaisoxazolyls which have already the properties of polymeric compounds.[41-43] The same method led to derivatives of a new condensed system, that of isoxazolo-(4,5:4',5')-isoxazole (**30**).[44]

[37] C. Weygand and E. Bauer, *Ann.* **459**, 123 (1927).
[38] A. Quilico and G. Speroni, *Gazz. chim. ital.* **76**, 148 (1946).
[39] A. Quilico, G. Gaudiano, and A. Ricca, *Gazz. chim. ital.* **87**, 638 (1957).
[40] G. Gaudiano and A. Ricca, *Gazz. chim. ital.* **89**, 587 (1959).
[41] G. Gaudiano, A. Quilico, and A. Ricca, *Tetrahedron* **7**, 24 (1959).
[42] A. Ricca and G. Gaudiano, *Atti accad. nazl. Lincei, Rend. Classe sci. fis. mat. e nat.* **28**, 211 (1960).
[43] G. Gaudiano, A. Ricca, and A. Quilico, *Gazz. chim. ital.* **90**, 1253 (1960).
[44] A. Quilico, G. Gaudiano, and L. Merlini, *Gazz. chim. ital.* **89**, 571 (1959).



(30)

Recently, Ricca[45] synthesized a number of diisoxazolylbenzenes (32) from phthalic aldehydes (31). This method is very promising and its



(31) (32)

versatility is illustrated by the synthesis of 3-chloroisoxazoles (33) from dichloroformoxime[46] and of 5-ethoxyisoxazoles from ethoxyacetylene.[47]

(33)

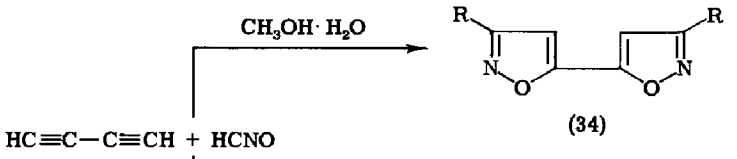
Syntheses of 4-substituted isoxazoles from β-diketones and hydroxamic acid chlorides were reported earlier.[1] A recent investigation has realt with the behavior in this reaction of malonic ester.[48]

The greatest attention is at present paid to the second variant which forms the 1—5 and 3—4 bonds, i.e., the addition reaction of nitrile

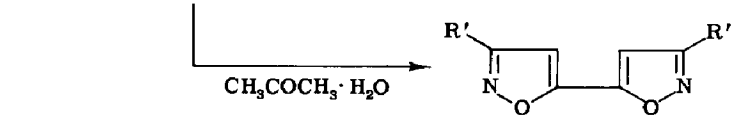
[45] A. Ricca, *Gazz. chim. ital.* **91**, 83 (1961).
[46] P. Bravo, G. Gaudiano, A. Quilico, and A. Ricca, *Gazz. chim. ital.* **91**, 47 (1961).
[47] G. Gaudiano, A. Ricca, and L. Merlini, *Gazz. chim. ital.* **89**, 2466 (1959).
[48] G. Stagno d'Alcontres and G. Lo Vecchio, *Gazz. chim. ital.* **91**, 1005 (1961).

oxides to multiple bonds. The simplest case is represented by the "fulminic synthesis" already mentioned.[1]

Of the few recent publications in this field two papers are noteworthy; these are Cramer's report on the synthesis of 3,3′-diisoxazolyl in 60–70% yield from acetylene and nitrogen oxides[49] and on the synthesis of a mixture of 5,5′-diisoxazolyls [**34**; **35**, R′ = $Me_2C(OH)$] from fulminic acid and diacetylene.[50]



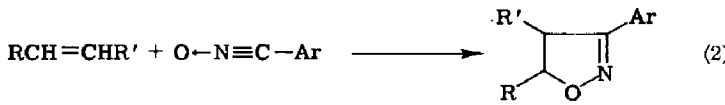
(34)



(35)

The general synthetic scheme starting from nitrile oxides, which condense with acetylenes to yield isoxazoles and with olefins to yield Δ^2-isoxazolines may be represented by Eqs. (1) and (2). The formation of isoxazolines with R′ = Cl or NO_2 is accompanied by ready elimination of R′H to give isoxazoles.[51] These syntheses have recently

(1)



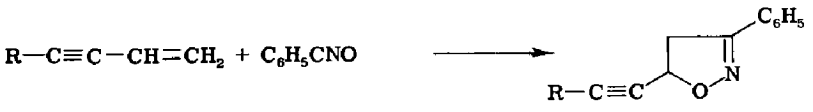
(2)

[49] R. D. Cramer, U. S. Patent 2,855,402 (7/10/1958); R. D. Cramer and W. R. McClellan, *J. Org. Chem.* **26**, 2976 (1961).
[50] P. Grünanger and E. Fabbri, *Atti accad. nazl. Lincei, Rend. Classe sci. fis. mat. e nat.* **26**, 235 (1959).
[51] P. Grünanger, *Gazz. chim. ital.* **84**, 359 (1954); *Atti accad. nazzl. Lincei, Rend. Classe sci. fis. mat. e nat.* **16**, 726 (1954).

been used extensively. The substituents at the multiple bond may be aromatic,[51] heterocyclic,[52] or alicyclic.[53,54] This method has led to the synthesis of chloromethyl isoxazoles,[55] 5-alkoxy isoxazoles,[56-58] acetals of isoxazol-5-ones,[59] and isoxazole as well as Δ^2-isoxazoline carbinols,[60] aldehydes,[61] ketones,[62,63] and carboxylic acids.[64,65] Multiple bonds may alternate with single bonds[66] or involve an allenic system,[67] each bond reacting in the latter case separately to yield spirobisisoxazolines (**36**).

(**36**)

In this synthesis the double bond displays more activity than does the triple bond, vinylacetylenes giving 5-ethynylisoxazolines (**37**)



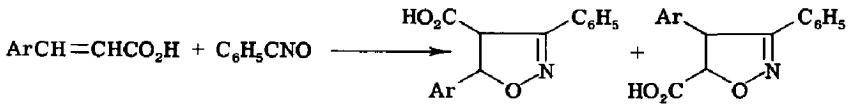
(**37**)

rather than vinylisoxazoles.[68] It turns out that for a double bond to

[52] P. Grünanger and L. Grasso, *Gazz. chim. ital.* **85**, 1271 (1955).
[53] N. Barbulescu and A. Quilico, *Gazz. chim. ital.* **91**, 326 (1961).
[54] P. Grünanger and M. R. Langella, *Gazz. chim. ital.* **91**, 1112 (1961).
[55] G. Stagno d'Alcontres and G. Cuzzocrea, *Atti soc. peloritana sci. fis. mat. e nat.* **3**, 179, 187 (1956–57).
[56] P. Grünanger, *Atti. accad. nazl. Lincei, Rend Classe sci. fis. mat. e nat.* **24**, 163 (1958).
[57] P. Grünanger and M. R. Langella, *Gazz. chim. ital.* **89**, 1784 (1959).
[58] T. Mukaiyma and T. Hata, *Bull. Chem. Soc. Japan* **33**, 1382 (1960).
[59] R. Scarpati and G. Speroni, *Gazz. chim. ital.* **89**, 1511 (1959).
[60] M. R. Langella and P. Grünanger, *Gazz. chim. ital.* **91**, 1449 (1961).
[61] G. Stagno d'Alcontres and G. de Giacomo, *Atti soc. peloritana sci. fis. mat. e nat.* **5**, 159, (1958–59); *Chem. Abstr.* **54**, 19646 (1960).
[62] P. Grünanger and S. Mangiapan, *Gazz. chim. ital.* **88**, 149 (1958).
[63] R. Scarpati and M. Rippa, *Gazz. chim. ital.* **88**, 804 (1958).
[64] P. Grünanger and P. Vita Finzi, *Gazz. chim. ital.* **89**, 1771 (1959).
[65] W. R. Vaughan and J. L. Spencer, *J. Org. Chem.* **25**, 1160 (1960).
[66] A. Quilico, P. Grünanger, and R. Mazzini, *Gazz. chim. ital.* **82**, 349 (1952).
[67] G. Stagno d'Alcontres and G. Lo Vecchio, *Gazz. chim. ital.* **90**, 1239 (1960).
[68] V. N. Chistokletov, A. T. Troshchenko, and A. A. Petrov, *Doklady Akad. Nauk S.S.S.R.* **135**, 631 (1960).

participate in the reaction its length must not exceed 1.35 Å.[69] Recently the behavior of various carbocyclic olefins has been extensively investigated, and it was found that, whereas semicyclic double bonds are reactive with rings of all sizes, the endocyclic double bonds react in cyclopentenes but fail to do so in cyclohexenes.[70] Of considerable interest is the work of Lo Vecchio and Monforte who demonstrated that the reactivity of nitrostyrenes and nitrophenylacetylenes with benzonitrile oxide decreased in the sequence m-$O_2NC_6H_4 > p$-$O_2NC_6H_4 > o$-$O_2NC_6H_4$, this being in good accord with the calculations by the molecular orbital method.[71]

The synthesis of isoxazolines usually takes the most thermodynamically favorable course to yield solely the more stable isomer. However, cinnamic acids (**38**) give not only isoxazoline-4-carboxylic acids (**39**) but also, as a by-product, the less stable isoxazoline-5-carboxylic acids (**40**)[72] which on heating undergo retro-addition.[73]

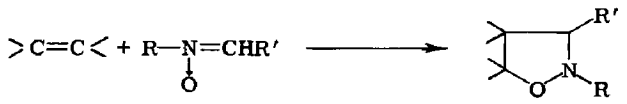


(**38**) (**39**) (**40**)

Recently the synthetic method involving formation of the **1**—**5** and **3**—**4** bonds has been extended to the preparation of the completely hydrogenated system of N-substituted isoxazolidines (**42**). This interesting reaction results from 1,3-dipolar addition of nitrones (**41**) to olefins.[74-77]

The double bond may be present in an acyclic or alicyclic compound, including dienes. The reaction is activated by the presence of

[69] G. Lo Vecchio, *Gazz. chim. ital.* **87**, 1413 (1957).
[70] N. Barbulescu, F. Grünanger, M. R. Langella, and A. Quilico, *Tetrahedron Letters* No. 3, p. 89 (1961).
[71] G. Lo Vecchio and P. Monforte, *Gazz. chim. ital.* **86**, 399 (1956); *Ann. chim. (Rome)* **46**, 76, 84 (1956).
[72] P. Monforte and G. LoVecchio, *Gazz. chim. ital.* **83**, 416 (1953).
[73] G. Lo Vecchio and P. Monforte, *Atti soc. peloritana sci. fis. mat. e nat.* **4**, 245 (1957–58); *Chem. Abstr.* **54**, 5618 (1960).
[74] N. A. Le Bel and Jong Jai Whang, *J. Am. Chem. Soc.* **81**, 6334 (1959).
[75] C. W. Brown, K. Marsden, M. A. T. Rogers, C. M. Tylor, and R. Wright, *Proc. Chem. Soc.* p. 254 (1960).
[76] G. R. Delpierre and M. Lamchen, *Proc. Chem. Soc.* p. 386 (1960).
[77] R. Grashey, R. Huisgen, and H. Leitermann, *Tetrahedron Letters* No. 12, p. 9 (1960).

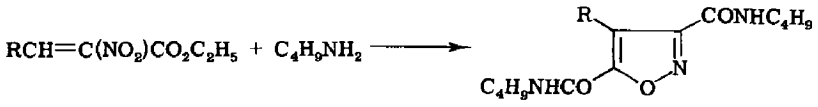


(41) (42)

electron-accepting substituents in the α-position to the double bond.[77]

The synthetic possibilities for isoxazoles and their hydrogenated derivatives by the formation of the 1—5 and 1—3 bonds are hardly exhausted; it is to be expected that the scope of these interesting reactions will be considerably enlarged.

Concluding this review of recent work on the synthesis of isoxazole derivatives, one should mention an interesting reaction, although at present it is of no preparative value. This reaction cannot, strictly speaking, be included in either of the two groups discussed in the foregoing because its mechanism is not yet known. It is a reaction of esters of α,β-unsaturated-α-nitroacids (43) with butylamine resulting in isoxazole-3,5-dicarboxylic amides (44).[78] There is some indication



(43) (44)

of the intermediate formation of nitroacetic acid though the reaction mechanism is far from elucidated.

III. The Structure and Physicochemical Properties of Isoxazole Derivatives

This decade has brought a number of investigations of the physicochemical properties of isoxazole derivatives and the elucidation of some details concerning their structure. The data obtained are in a good agreement with the conceptions as to the structure of isoxazole as reviewed by Barnes.[1] We shall therefore be concerned only with recent work.

The detailed study of dipole moments of isoxazole and its homologs,[79] arylisoxazoles,[80] and isoxazole carboxylic acids[81,82] has substantiated the conclusion that the carbon atoms C-3, C-4, and C-5 of the isoxazole ring are in different environments. Therefore, the mutual influence of the heterocyclic nucleus and the substituents depend on the position of the latter. The interaction between a substituent at C-5 and the ring, where the conjugation with the isoxazole nucleus is strong, is more pronounced than the interaction of a substituent at C-3. The conjugation is more pronounced for phenyl groups than for methyl groups. These data are in accord with the pK_a's for aminoisoxazoles[83] and isoxazole carboxylic acids,[84] which suggest that the isoxazole nucleus is a weaker electron donor than the benzene nucleus, this property decreasing at the isoxazole carbon atoms in the order C-4 > C-5 ~ C-3.

The spectra of isoxazoles have recently been examined in detail. Pino *et al.* investigated the UV spectra of isoxazole and the methylisoxazoles. These spectra revealed characteristic shifts in the maxima depending on the number and position of methyl groups.[85] Such regularities are characteristic only for aromatic systems. The shift is most marked for a C-4 methyl group, and is absent for a C-3 methyl group.

This again substantiates the order of nucleophilicity of the carbon atoms of the isoxazole nucleus, as already mentioned. The UV spectra of phenylisoxazoles present a similar regularity.[86] Quilico *et al.* have investigated the UV spectra of diisoxazolyls and found a different degree of conjugation for 3,3′-, 3,5′-, and 5,5′-diisoxazolyls.[41] In the last case, as with a 5-substituted isoxazole, the interaction between the rings is most complete. The UV spectra of polyisoxazolyls,[36,41,43] of arylalkoxyisoxazoles,[57] and of other substituted isoxazoles[46] have also been studied.

[78] S. Umezawa and S. Zen, *Bull. Chem. Soc. Japan* **33**, 1016 (1960).

[79] G. Speroni, P. Pino, and L. Mori, *Gazz. chim. ital.* **82**, 269 (1952).

[80] G. Tappi and C. Springer, *Gazz. chim. ital.* **70**, 190 (1940).

[81] G. Speroni and L. Mori, *Atti accad. nazl. Lincei, Rend. Classe sci. fis. mat. e nat.* **12**, 704 (1952).

[82] G. Speroni and P. Pino, *Atti. accad. nazl. Lincei, Rend. Classe sci. fis. mat. e nat.* **13**, 39 (1952).

[83] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 51 (1961).

[84] A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta* **17**, 238 (1961).

[85] P. Pino, G. Speroni, and V. Fuga, *Gazz. chim. ital.* **84**, 759 (1954).

[86] P. Pino and G. Speroni, *Rend. ist. lombardo sci., Pt. I.* **88**, 331 (1955); *Chem. Abstr.* **50**, 6189 (1956).

The IR spectra of isoxazole derivatives have been extensively investigated.[36,43,87-89] The most exhaustive and precise data, including both the characteristic frequencies and intensities, were reported by Katritzky and Boulton[83,84,90] for isoxazole and its homologs, aryl- and alkoxy-isoxazoles, acids, and some other derivatives.

The frequency of the IR carbonyl stretching band of the isomeric isoxazole carboxylates corresponds rather well with the degree of conjugation at the 3-, 4-, and 5-positions of the isoxazole nucleus with substituents as mentioned before. The foregoing UV and IR spectral and dipole moment data allow the deduction of close regularities, but these conclusions differ somewhat from the results of molecular orbital calculations which point to the following conjugation order: C-4 > Ph > C-5 > C-3.[84] The results obtained reveal that the isoxazole ring is a very weak electron donor at the 3-position.

Spectroscopic methods have been successfully applied to the elucidation of some details of the fine structure of isoxazole derivatives. Thus IR spectra revealed steric hindrance in the case of some 3,4,5-trisubstituted isoxazoles[84]; for phenylisoxazoles this results in the nonplanarity of the benzene and isoxazole rings and decreasing mutual interaction.

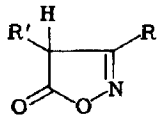
The investigation of UV and IR spectra of isoxazolines[70,91,92] has shown them to be the Δ^2-isomers. The IR spectra of isoxazolidin-3-ones were investigated in connection with the chemistry of cycloserine.[93]

The application of spectroscopic methods to the study of tautomerism proved especially fruitful.[83,90,94] The tautomerism of hydroxy and amino derivatives of isoxazole is of great interest to the chemistry of isoxazole; this subject, as well as the tautomerism of functional derivatives of other five-membered heterocycles, has been reviewed by Katritzky and Lagowski.[95] We shall therefore only

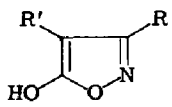
[87] S. Califano, F. Piacenti, and G. Speroni, *Spectrochim. Acta* **15**, 86 (1959).
[88] E. Borello, *Gazz. chim. ital.* **89**, 1437 (1959).
[89] A. R. Katritzky, *Quart. Revs. (London)* **13**, 353 (1959).
[90] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).
[91] R. P. Barnes, G. E. Pinkney, and G. McK. Phillips, *J. Am. Chem. Soc.* **76**, 276 (1954).
[92] G. W. Perold, A. P. Steyn, and F. V. K. von Reiche, *J. Am. Chem. Soc.* **79**, 462 (1957).
[93] V. G. Vinokurov, V. S. Troitskaya, and N. K. Kochetkov, *Zhur. Obshchei Khim.* **31**, 205 (1961).
[94] A. R. Katritzky and S. Øksne, *Tetrahedron* **18**, 777 (1962).
[95] A. R. Katritzky and J. M. Lagowski, *Advances in Hetero. Chem.* **2**, 27 (1963).

briefly mention some of the main conclusions concerning these important investigations.

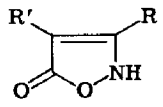
The structural studies of isoxazol-5-ones have shown that these compounds can be found in one of the three tautomeric forms (**45**–**47**).[59,90,96-98] It has been established that the 3-methyl-4-benzoyl



C—H - form
(45)



O—H - form
(46)



N—H - form
(47)

derivative exists both as a solid or in solution in the OH form, whereas the crystalline 4-substituted 3-phenylisoxazolones are to be found in the NH form. In solutions the latter compounds can be in the NH or in the CH forms or in their mixture, the increased polarity of the solvent resulting in increasing NH-isomer content.[90] The hydroxy structure has been proved for 3-hydroxy-5-phenylisoxazole.[46]

Aminoisoxazoles exist only in the amino form, independent of the position of the amino group in the ring.[83] It will be noted that the isomeric 3,5-aminoisoxazolones possess an amino and a carbonyl group.[99]

IV. The Reactions of Isoxazole Derivatives with the Retention of the Heterocyclic Nucleus

To understand the general character of the isoxazole nucleus and to establish its place among the other heterocyclic aromatic systems, it is of the greatest interest to investigate the reactions of isoxazole derivatives in which the heterocyclic nucleus remains intact, especially substitution reactions.

A characteristic peculiarity of isoxazole derivatives is the relatively facile ring cleavage under suitable conditions, and this is a severe limitation on reactions of substitution in the isoxazole series. The best, though as yet inadequately, studied reactions, are the

[96] I. Ya. Postovskii and S. V. Sokolov, *Zhur. Obshchei Khim.* **29**, 3446 (1959).
[97] S. V. Sokolov and I. Ya. Postovskii, *Zhur. Obshchei Khim.* **30**, 600 (1960).
[98] N. K. Kochetkov, S. D. Sokolov, L. D. Ashkinadze, and M. A. Chlenov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, No. 5, in press (1963).
[99] C. L. Bell, C. N. V. Nambury, and L. Bauer, *J. Org. Chem.* **26**, 4923 (1961).

electrophilic substitutions which are reviewed at the beginning of this section.

The nucleophilic substitution reactions are still more limited in scope owing to the instability of the isoxazole ring toward nucleophilic reagents. Homolytic reactions appear to be unknown though some of the reactions being studied are possibly of this type. Besides those reactions which are characteristic of the reactivity of the isoxazole nucleus itself, we shall consider in this section some substitution reactions in the side chain: organomagnesium synthesis in the isoxazole series, condensation reactions of the methyl groups of methylisoxazoles, and finally some miscellaneous reactions.

A. Electrophilic Substitution Reactions

It should be expected that the orientation and rate of electrophilic substitution in the isoxazole nucleus would be affected by both hetero atoms. Because of the electron-accepting effect of the nitrogen atom, electrophilic substitution of the isoxazole nucleus should proceed less readily than in the case of benzene and should occur essentially at the position β to the nitrogen atom, just as in pyridine and other azoles. Simultaneously the electron-donating oxygen atom should facilitate such reactions in isoxazole as compared with the substitution in pyridine. These predictions are confirmed by the available experimental evidence.

Isoxazoles are known at present to undergo the following electrophilic substitution reactions: nitration, sulfonation, halogenation, chloroalkylation, hydroxymethylation, and mercuration. Repeated attempts to effect the Friedel-Crafts reaction in the isoxazole series in the authors' laboratory failed. The isoxazole nucleus seems not active enough to react with weak electrophilic reagents.

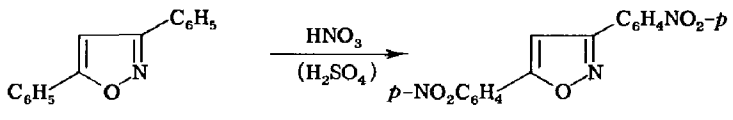
1. *Nitration*

The first electrophilic substitution reaction studied in the isoxazole series was the nitration of 3,5-dimethylisoxazole reported by Morgan and Burgess in 1921.[100] The reaction occurs smoothly on heating with mixed nitric and sulfuric acids at 100°C and leads to the 4-nitro derivative in 86% yield.

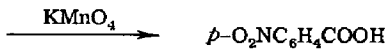
This reaction was later extended to 3- and 5-methylisoxazoles,[101]

[100] G. T. Morgan and H. Burgess, *J. Chem. Soc.* **119**, 697 (1921).
[101] A. Quilico and C. Musante, *Gazz. chim. ital.* **71**, 327 (1941).

3-phenyl-, 3-methyl-5-phenyl-, and 3,5-diphenyl-isoxazoles.[102,103] Alkylisoxazoles are converted to 4-nitro derivatives, whereas phenylisoxazoles (e.g. **48**) are nitrated in the para position of the phenyl nuclei as proved by the degradative oxidation of nitro derivatives (**49** → **50**). Ethyl 5-phenylisoxazole-3-carboxylate reacts similarly.[104]



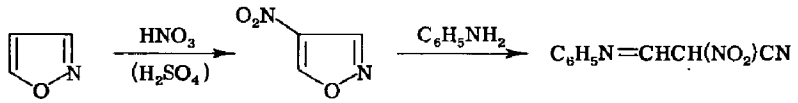
(48) (49)



(50)

Different results were obtained by Kochetkov and Khomutova.[105] After nitrating 5-phenylisoxazole, they isolated two nitro derivatives, one of which contained a nitro group in the phenyl nucleus, the other one in the isoxazole ring. It is to be expected that the nitration of other phenylisoxazoles results in some second isomer that has not been isolated due to a negligible yield. It will also be noted that the nitration of arylisoxazoles proceeds faster and under milder conditions than necessary for the alkyl derivatives.

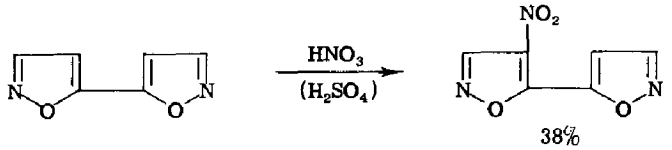
It is most difficult to nitrate isoxazole itself. 4-Nitroisoxazole (**51**) is formed only under strictly controlled conditions (35–40°C), and in but 3.5% yield.[106] Its structure was proved by reaction with aniline (see Section V,A) to give nitrocyanoacetaldehyde anil (**52**).



(51) (52)

[102] C. Musante, *Gazz. chim. ital.* **72**, 537 (1942).
[103] C. Musante, *Farm. sci. e tec. (Pavia)* **6**, 32 (1951); *Chem. Abstr.* **45**, 5879 (1951).
[104] S. Cusmano, *Gazz. chim. ital.* **69**, 214 (1939).
[105] N. K. Kochetkov and E. D. Khomutova, *Zhur. Obshchei Khim.* **28**, 359 (1958).
[106] N. K. Kochetkov and E. D. Khomutova, *Zhur. Obshchei Khim.* **29**, 535 (1959).

It also proved possible to nitrate 5,5′- (**53**) and 3,3′-diisoxazolyls[107,108]; the former yields successively (**54**) and (**55**).



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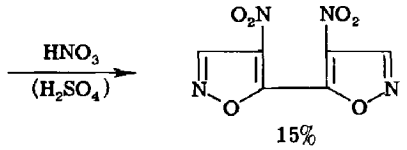
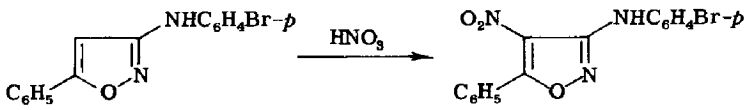


(55)

There is but little information concerning the nitration of isoxazoles with functional substituents. The fact that dinitro derivatives are not formed indicates that electron-accepting substituents completely deactivate the nucleus. On the other hand, electron-donating substituents strongly enhance nitration. Thus, the nitration of 3-anilino-5-phenylisoxazole proceeds extremely readily,[109,110] the amino group activating both nuclei. If a halogen atom is placed at the para position of the benzene ring, then the isoxazole ring is nitrated first, cf. **56** → **57**.



(56) (57)

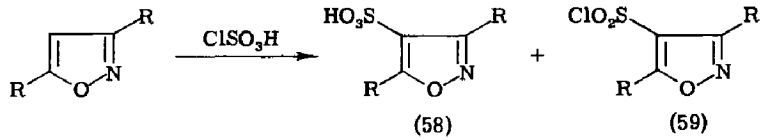
4-Nitroisoxazoles can be readily reduced to 4-aminoisoxazoles. Stannous chloride in hydrochloric acid is usually used,[101,107] but better results are obtained with aluminum amalgam.[83,100]

[107] R. Fusco and S. Zumin, *Gazz. chim. ital.* **76**, 223 (1946).
[108] G. Gaudiano, A. Ricca, and A. Quilico, *Atti accad. nazl. Lincei, Rend. Classe sci. fis. mat. e nat.* **26**, 164 (1959).
[109] D. E. Worral, *J. Am. Chem. Soc.* **59**, 933 (1937); *ibid.* **60**, 1198 (1938).
[110] D. E. Worral and E. Lavin, *J. Am. Chem. Soc.* **61**, 104 (1939).

2. *Sulfonation*

Sulfonation of isoxazoles has been less extensively studied than nitration. This is possibly due to the difficulty encountered in isolating isoxazolesulfonic acids and to the ambiguous reaction course.

It was not until 1940 that the sulfonation of alkylisoxazoles by heating them with chlorosulfonic acid was reported.[111,112] This gave a mixture of isoxazole-4-sulfonic acids (**58**) and their acid chlorides (**59**). The position of the sulfonic group in derivatives of monomethyl isoxazoles has been proved by nucleophilic cleavage of the isoxazole ring (**60** → **61**). Recently it proved possible to sulfonate isoxazole



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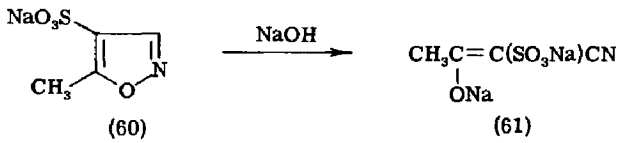
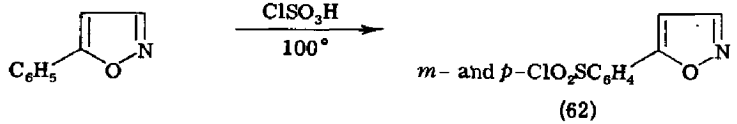


(60) (61)

itself; the 4-sulfonic acid was obtained in 17% yield[106]: the reaction occurs only under more drastic conditions (20% oleum) than the sulfonation of alkylisoxazoles.

As to arylisoxazoles, it was only in 1961 that Woodward *et al.*[113] investigated the sulfonation of 5-phenylisoxazole. In contrast to nitration, only the phenyl nucleus is sulfonated to yield a mixture of *m*- and *p*-aryl sulfonic acid chlorides (**62**) in a 2:1 ratio.

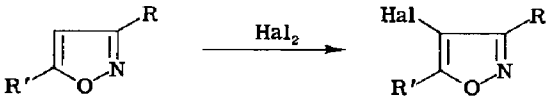


(62)

[111] A. Quilico and R. Justoni, *Gazz. chim. ital.* **70**, 1 (1940).
[112] A. Quilico and R. Justoni, *Gazz. chim. ital.* **70**, 11 (1940).
[113] R. B. Woodward, R. Olofson, and H. Mayer, *J. Am. Chem. Soc.* **83**, 1010 (1961).

3. *Halogenation*

Halogenation of isoxazoles was also first performed with alkyl homologs.[114] When treated with chlorine or bromine and exposed to sunlight or heated, the isoxazole nucleus undergoes halogenation in the 4-position (**63** → **64**).

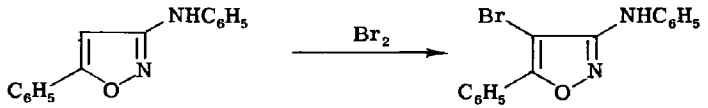


(63) (64)

The chlorination of 3-isopropenyl-5-methylisoxazole and of dimethyl-(5-methylisoxazol-3-yl)carbinol[10] and, recently, the bromination of 5- and 3-phenylisoxazoles and unsubstituted isoxazole[105,106,115] have also been studied. Reaction is effected by heating in the presence of powdered iron and gives 4-bromoisoxazoles (**63** → **64**, Hal = Br; R,R′ = H, Ph).

More recently Pino *et al.* have treated isoxazole with bromine without adding iron and obtained 4-bromoisoxazole in a 42% yield.[116] The stepwise bromination of 5,5′- and 3,3′-diisoxazolyls gives higher yields (70–80%).[108]

As with other electrophilic substitution reactions, there is practically no work available on the halogenation of isoxazoles with functional substituents. The only instance that indicates that the general pattern holds true here is the extremely rapid bromination of 3-anilino-5-phenylisoxazole (**65**), in which the isoxazole ring is the first to react with 1 mole of bromine, yielding **66**.[109,110]



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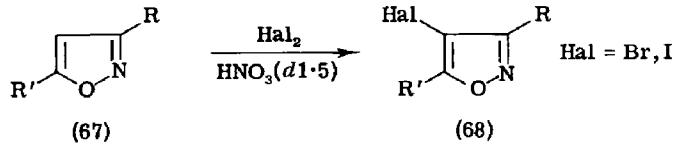
Kochetkov *et al.* have recently developed a general method for the synthesis (**67** → **68**) of 4-iodo- and 4-bromo-isoxazoles involving the

[114] A. Quilico and R. Justoni, *Rend. ist. lombardo sci. Pt. I* **69**, 587 (1936); *Chem. Zentr. I* p. 1424 (1937).
[115] N. K. Kochetkov and E. D. Khomutova, *Zhur. Obshchei Khim.* **30**, 1269 (1960).
[116] P. Pino, F. Piacenti, and G. Fatti, *Gazz. chim. ital.* **90**, 356 (1960).



(67) (68)

action of halogens in the presence of concentrated nitric acid (d 1.5)[8,117]; this method of halogenating isoxazoles, similar to the conventional halogenation method for aromatic compounds, is up to now the only general method for obtaining iodides and it also gives higher yields of bromo derivatives. Notably, substitution in arylisoxazoles occurs only in the isoxazole nucleus, as proved by the oxidation of the halogeno derivatives with potassium permanganate.

The isoxazole nucleus is also halogenated in the 4-position by *N*-bromosuccinimide provided there is no substituent in this position.[118] This reaction does not proceed homolytically, as might have been expected, and appears to represent a simple electrophilic substitution by the bromine cation. Similar cases have been previously described for the bromination of certain aromatic compounds with *N*-bromosuccinimide.[119]

4. *Chloroalkylation and Hydroxymethylation*

It is only recently that the chloromethylation reaction, well known in the benzene series, has been extended to isoxazoles.[120,121] It has been thereby found that this reaction results in 4-chloromethyl derivatives (**69**), their yield decreasing as follows: 5-phenyl > 3,5-dimethyl > 5-methyl > 3-methyl isoxazoles > isoxazole. To prove the position of the chloromethyl group these compounds were oxidized to the known isoxazole-4-carboxylic acids (**70**). It is especially noteworthy that pyridine and its homologs do not undergo chloromethylation.

[117] N. K. Kochetkov, S. D. Sokolov, and N. M. Vagurtova, *Zhur. Obshchei Khim.* **31**, 2326 (1961).
[118] N. K. Kochetkov, S. D. Sokolov, and N. M. Vagurtova, *Zhur. Obshchei Khim.* **32**, 325 (1962).
[119] S. D. Ross, M. Finkelstein, and R. C. Peterson, *J. Am. Chem. Soc.* **80**, 4327 (1958). Sing-tuh Voong and Kun-yuen Chiu, *Sci. Sinica (Peking)* **9**, 748 (1960).
[120] N. K. Kochetkov, E. D. Khomutova, M. Ja. Karpeysky, and R. M. Khomutov, *Zhur. Obshchei Khim.* **27**, 3210 (1957).
[121] N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevsky, *Zhur. Obshchei Khim.* **28**, 2376 (1958).

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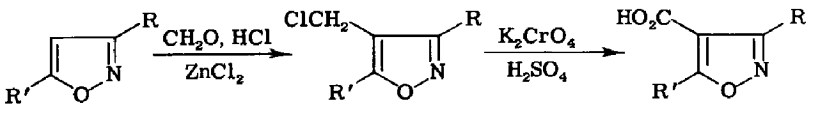
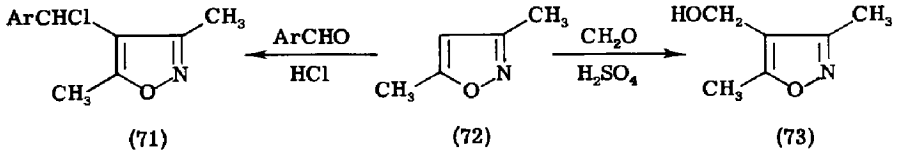
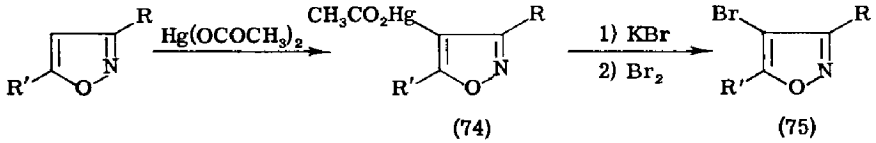


Further, isoxazole derivatives were subjected to two related reactions. 3,5-Dimethylisoxazole was found to react in the presence of dry hydrogen chloride with aromatic aldehydes (chlorobenzylation, **72**→**71**),[122] and with formaldehyde in the presence of sulfuric acid it undergoes hydroxymethylation (**72**→**73**).[123]



5. *Mercuration*

Recently, Kochetkov and Khomutova[105,115] have reported on the mercuration of isoxazoles with mercuric acetate. The reaction occurs quite smoothly, more readily than for benzene derivatives and results in a 90–100% yield of 4-acetoxymercury derivatives (**74**) whose structure was proved by converting them to known 4-bromoisoxazoles (**75**). Under these reaction conditions isoxazole itself is oxidized by mercuric acetate, mercurous salts being thereby produced.



Whereas most reactions in the isoxazole series are undoubtedly those of electrophilic substitution, mercuration of isoxazoles, as well as some cases of mercuration of aromatic compounds, could be considered as homolytic reactions. However, the ready mercuration of

[122] N. K. Kochetkov, S. D. Sokolov, and V. E. Zhvirblis, *Zhur. Obshchei Khim.* **30**, 3675 (1960).

[123] N. K. Kochetkov, S. D. Sokolov, and V. E. Zhvirblis, *Zhur. Vsesoyuz. Khim. Obshchestva im. D. I. Mendeleeva* **6**, 466 (1961).

isoxazoles and the formation of 4-mercuric derivatives point to the electrophilic character of this reaction. It should be mentioned that the mercuration of pyridine derivatives also proceeds by the electrophilic mechanism.[124]

6. *General Discussion*

If one bears in mind the peculiarities noted at the beginning of this section, the electrophilic substitution reactions which are known at present in the isoxazole series proceed in accordance with general pattern of electrophilic substitution in aromatic systems.

In the reactions of electrophilic substitution, isoxazole is far less active than the five-membered heterocycles with one hetero atom and pyrazole. It is closer to pyridine, but more reactive.

The presently known electrophilic substitution reactions all occur at the 4-position of the isoxazole nucleus, corresponding to the β-position in pyridine. Thus the influence of the nitrogen atom is predominant. The introduction of alkyl and, particularly, aryl substituents into the isoxazole nucleus markedly increases its reactivity (on the other hand, during nitration and sulfonation the isoxazole nucleus also activates the phenyl nucleus).

This activation is more pronounced on the introduction of stronger electron-donor substituents, but this point is not yet sufficiently studied. The isoxazole ring is unsymmetrical, and the activating effect of the substituent depends on its position. The available evidence shows that a substituent at C-5 activates the nucleus (or rather the 4-position) more strongly than does a substituent at C-3.

The mechanisms of the electrophilic substitutions in the isoxazole nucleus have not yet been studied. They should not differ fundamentally from those usually accepted for the substitution of aromatic systems but the structural specificity of the isoxazole ring might give rise to some peculiarities, as recently specially discussed.[117] One important point is that isoxazole shows a clearcut tendency to form coordination compounds. Just as pyridine and other azoles, isoxazoles coordinate with halogens[114,117] and the salts of heavy metals, for example of cadmium,[125,126] mercury,[126,127] zinc.[128] Such coordination

[124] M. W. Swaney, M. J. Skeeters, and R. N. Shreve, *Ind. Eng. Chem.* **32**, 360 (1940).

[125] L. Claisen, *Ber. deut. chem. Ges.* **36**, 3664 (1903).

[126] L. Claisen, *Ber. deut. chem. Ges.* **59**, 144 (1926).

[127] W. R. Dunstan and T. S. Dymond, *J. Chem. Soc.* **59**, 410 (1891).

[128] P. Billon, *Compt. rend. acad. sci.* **182**, 584 (1926).

compounds could directly participate in the reaction and, by polarizing the isoxazole system, could change, and in particular accelerate, the reaction course.

Mercuration and chloromethylation reactions as well as halogenation seem to proceed with preliminary coordination followed by substitution in the coordination compound.[117] Such reactions as nitration and sulfonation in concentrated acids appear to proceed differently as evidenced by the substitution of the phenyl nucleus on nitration and by the sulfonation of phenylisoxazoles.

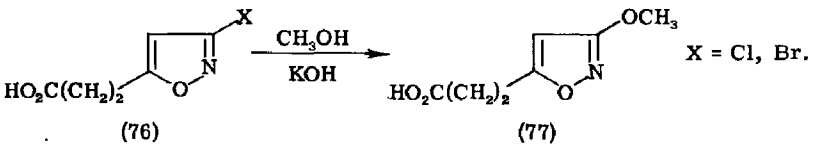
Similar peculiarities had been noted previously on nitration of phenylpyridines[129] and pyrazoles[103,130] as well as on sulfonating phenylpyrazoles.[131]

B. Nucleophilic Substitution Reactions

No direct nucleophilic substitution of the hydrogen atoms in the isoxazole nucleus α or γ to the nitrogen is as yet known. Thus, the Chichibabin reaction fails in the isoxazole series because of the cleavage of the heterocyclic nucleus under these conditions.[27] It is the lability of the isoxazole ring toward nucleophilic reagents that makes the chemical behavior of isoxazole fundamentally different from that of pyridine.

The substitution of fairly labile nucleophilic groups (halogen, methoxy group) in the 3- and 5-positions, and the noncatalytic substitution of the diazonium group at C-4, are to be considered as nucleophilic substitution reactions. As in the benzenoid series, these reactions are believed to proceed in the former case by the S_N2 mechanism and in the latter by the S_N1 mechanism.

In 1909, Thiele and Landers reported the synthesis of β-(3-methoxyisoxazol-5-yl)-propionic acid (**77**), from the corresponding chloride or bromide (**76**).[12] In 1961, a similar reaction was reported for 3-chloro-5-arylisoxazoles, enabling the synthesis of 3-hydroxy-5-phenyl-

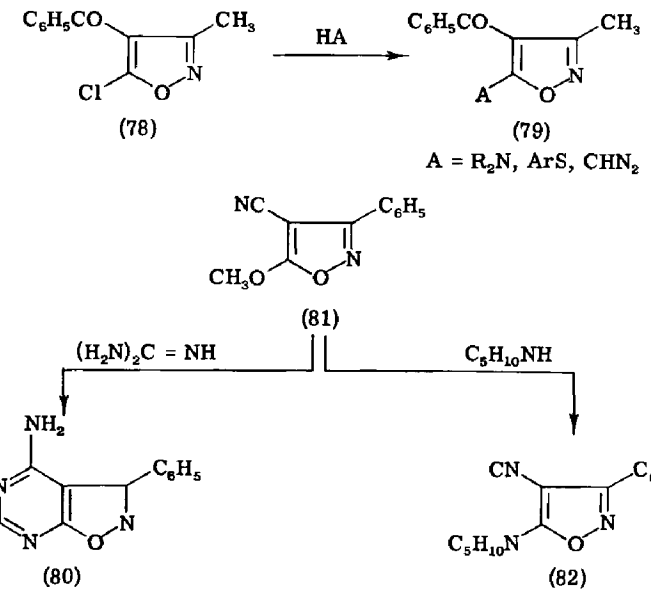


(76) (77)

[129] R. Forsyth and F. L. Pyman, *J. Chem. Soc.* p. 2912 (1926).
[130] D. Dal Monte Casoni, *Ann. chim. (Rome)* **48**, 783 (1958).
[131] W. J. Barry, *J. Chem. Soc.* p. 3851 (1961).

isoxazole, and of 3,3′-dichloro-5,5′-diisoxazolyls.[46] These reactions occur much more readily than the analogous nucleophilic substitution in the benzene series, resembling in this respect 2- and 4-halogenopyridines.

The nucleophilic substitution of a halogen atom at C-5 in the isoxazole nucleus without further functional substituents is so far unknown, but recently reports appeared on the nucleophilic substitution reactions at C-5 in isoxazole derivatives with benzoyl (**78**→**79**), ester, and cyano groups (**81**→**80**, **82**) in the 4-position.[30,96,132,133]

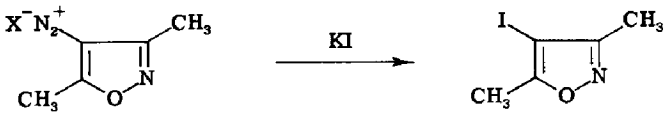


It is of interest that these reactions exhibit stronger activation of the substituent at C-5 by a neighboring electron-acceptor group compared with the corresponding ortho-substituted benzene. This is possibly owing either to the effect of the nitrogen hetero atom or to a weaker delocalization of multiple bonds in the heterocyclic nucleus.

The noncatalytic substitution of a 4-diazonium group by nucleophiles, which has proved widely useful in this series, is probably an example of a unimolecular nucleophilic substitution. The first example

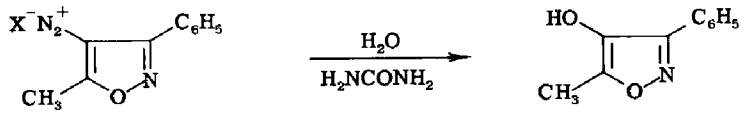
[132] G. Speroni and E. Giachetti, *Gazz. chim. ital.* **83**, 192 (1953).
[133] S. V. Sokolov, Dissertation, Leningrad, 1961.

of such a reaction was provided by the synthesis of 3,5-dimethyl-4-iodoisoxazole (**83** → **84**).[134] Later this route was extended to various



(83) (84)

4-chloroisoxazoles[10,101,107] and to 3-phenyl-4-hydroxy-5-methylisoxazole (**85** → **86**).[10]



(85) (86)

C. Substitution in the Side Chain of Isoxazoles

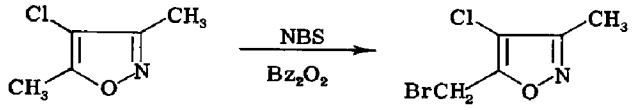
Reactions involving the introduction and substitution of functional groups in the side chain of isoxazole derivatives are of synthetic value and have been used to synthesize various substituted isoxazoles.

This section will merely deal briefly with new data concerning a more specific topic, that of homolytic halogenation of the side chain and substitution of the halogen atom in the side chain.

1. *Homolytic Halogenation*

The first report on homolytic halogenation of methylisoxazoles was published recently by Kochetkov and Sokolov.[9,118] As mentioned previously (Section IV,A,3), isoxazoles not containing substituents at the 4-position are substituted by *N*-bromosuccinimide or sulfuryl chloride in the nucleus by the electrophilic mechanism. With methylisoxazoles involving a substituent at C-4, the possibility of effecting, and the course of, homolytic bromination of the methyl group depends on its position in the ring and on the substituent at C-4. Thus 3-methyl-4-chloro-5-phenyl-, 3,5-dimethyl-4-benzoyl-, and 3,5-dimethyl-4-nitro-isoxazoles do not react with *N*-bromosuccinimide. Under these conditions 3,5-dimethyl-4-chloroisoxazole (**87**) is brominated in the methyl group at C-5 and various 4-methylisoxazoles in the methyl group (cf. **89** → **90**). 3,5-Diphenyl-4-methylisoxazole also reacts

[134] G. T. Morgan and H. Burgess, *J. Chem. Soc.* **119**, 1546 (1921).



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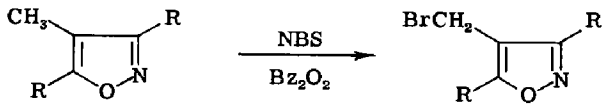


(89) (90)

readily with bromine and with sulfuryl chloride in the presence of benzoyl peroxide to yield 4-halogenomethyl derivatives.

Thus the activity of the methyl groups in this reaction decreases in the series C-4 > C-5 > C-3. This may be considered as evidence of the inhibiting effect of the nitrogen hetero atom on the radical substitution in methyl groups at C-3 and, to a lesser extent, at C-5 (compare the effect of the heterocyclic nitrogen in the pyridine and azole series[135]) and of a similar effect of the electron-accepting substituents in the 4-position on the methyl group at C-5.

2. *Substitution of the Halogen in Halogenomethylisoxazoles*

Nucleophilic substitution of the halogen atom of halogenomethylisoxazoles proceeds readily; this reaction does not differ essentially from that of benzyl halides. One should note the successful hydrolysis of 4-chloromethyl- and 4-(chlorobenzyl)-isoxazoles by freshly precipitated lead oxide, a reagent seldom used in organic chemistry.[121,122] Other halides,[18] ethers,[118,120] and esters[136] of the isoxazole series have been obtained from 3- and 4-halogenomethylisoxazoles, and 3-chloromethylisoxazole has been reported in the Arbuzov rearrangement.[137] Panizzi has used dichloromethylisoxazole derivatives to synthesize isoxazole-3- and isoxazole-5-aldehydes.[138]

[135] N. P. Buu-Hoi, *Ann.* **556**, 1 (1944); R. Gompper and H. Rühle, *Ann.* **626**, 83, 92 (1959).

[136] N. K. Kochetkov and A. Ja. Khorlin, *Zhur. Obshchei Khim.* **25**, 1212 (1955).

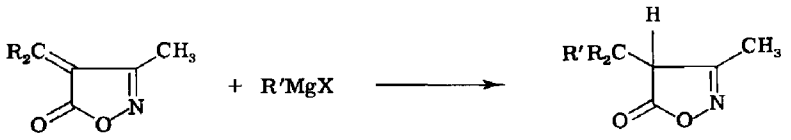
[137] B. A. Arbuzov and V. M. Zoroastrova, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* p. 806 (1954).

[138] L. Panizzi, *Gazz. chim. ital.* **72**, 99 (1942); *ibid.* **73**, 99 (1943).

D. Grignard Synthesis

Organometallic synthesis in the isoxazole series is so far exemplified only by the Grignard reaction; both the action of organomagnesium compounds on isoxazole derivatives and the use of organomagnesium compounds with an isoxazole ring have been described. The instability of the isoxazole ring toward those organomagnesium compounds that behave as nucleophiles and reducing agents complicates the Grignard reaction in this series. However, it has often been successfully applied to produce isoxazole alcohols from ketones[139-141] and from isoxazole esters[10] as well as to obtain isoxazole ketones from the corresponding nitriles.[142-144]

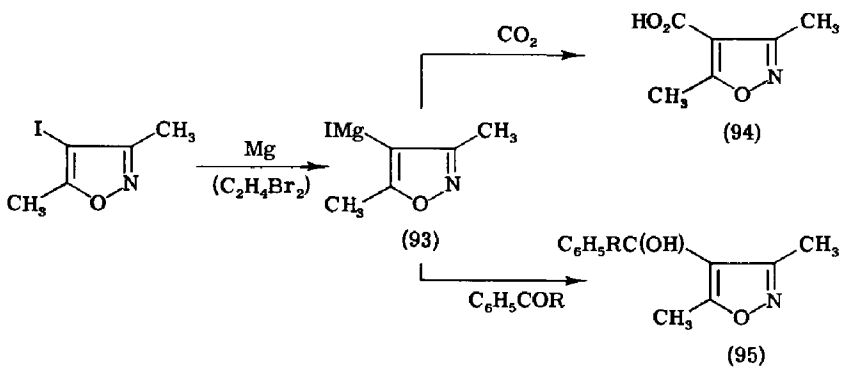
An interesting example of the organomagnesium synthesis is to be found in the use of 1,4-addition of the Grignard reagent to 4-alkylideneisoxazol-5-ones (**91**) to prepare saturated isoxazol-5-ones (**92**).[145]



(91) (92)

Less known and, it seems, of more limited scope is the use of organomagnesium compounds containing an isoxazole ring reported only recently.[8,146] 3,5-Disubstituted 4-iodo- and 4-bromo-isoxazoles react with magnesium under the conditions of an "entrainment reaction" in the presence of ethyl bromide or, better, dibromoethane. The isoxazolyl magnesium halides (e.g. **93**) formed thereby may be used in typical Grignard syntheses, for instance to prepare isoxazole-4-carboxylic acids (**94**) or the corresponding carbinols (**95**). Iodides give considerably better results than bromides (see Section V,C), but 4-iodo-5-substituted isoxazoles undergo predominant cleavage of the isoxazole ring. This is the main obstacle that severely limits the

[139] E. P. Kohler, *J. Am. Chem. Soc.* **46**, 1733 (1924); *ibid.* **47**, 3030 (1925).
[140] M. Freri, *Gazz. chim. ital.* **61**, 312 (1931).
[141] A. Quilico, G. Speroni, and E. Galeffi, *Gazz. chim. ital.* **69**, 508 (1939).
[142] A. Quilico and M. Freri, *Gazz. chim. ital.* **62**, 436 (1932).
[143] C. Musante, *Gazz. chim. ital.* **70**, 685 (1940).
[144] M. Giannini and M. Fedi, *Farmaco (Pavia), Ed. sci.* **13**, 835 (1958).
[145] L. Panizzi, *Gazz. chim. ital.* **76**, 44 (1946).
[146] N. K. Kochetkov and S. D. Sokolov, *Zhur. Obshchei Khim.* **33**, 1196 (1963).

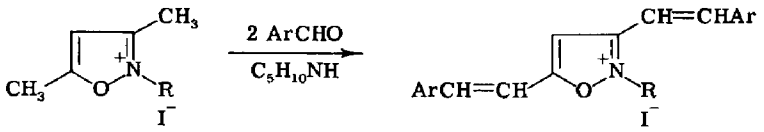


preparation and use of organomagnesium derivatives of isoxazole. The proportion of the competitive cleavage reaction of the ring depends on the nature of the substituents in the isoxazole nucleus, including that of the halide (see Section V,C).

Only a single example is as yet known of an organomagnesium compound involving the side chain, namely (3,5-dimethylisoxazol-4-yl)methylmagnesium chloride.[146]

E. Condensation Involving Activated Methyl Groups of Methylisoxazoles

A characteristic feature of picolines and many azoles is the well-known ability of methyl (and corresponding methylene) groups to undergo condensation of the aldol, crotonic, and Michael type. This is especially pronounced in the quaternary salts of these heterocycles where it occurs under comparatively mild conditions. Such condensations are not unknown for alkylisoxazoles. Lampe and Smolinska[147,148] were the first to describe the condensation of the quaternary alkyl iodides of 3,5-dimethyl- (**96**) and 3-methyl-5-phenylisoxazole with



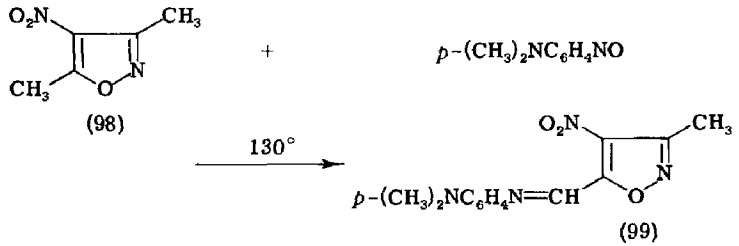
(96) (97)

[147] W. Lampe and J. Smolinska, *Roczniki Chem.* **28**, 163 (1954); *ibid.* **29**, 934 (1955).
[148] W. Lampe and J. Smolinska, *Bull. acad. polon. sci.* **6**, 481 (1958).

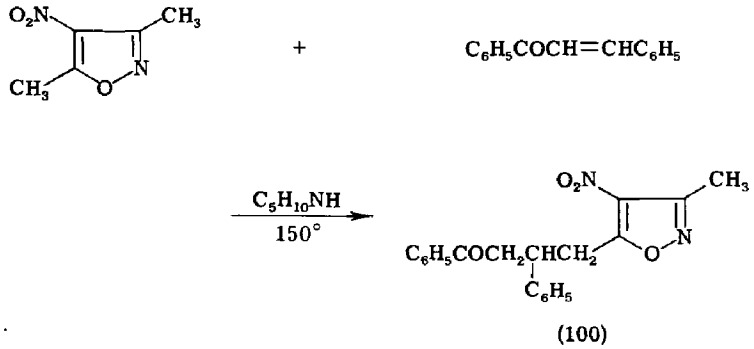
aromatic aldehydes; the reaction (**96** → **97**) proceeds readily in the presence of piperidine.

Among electron-accepting groups only the nitro group proved to be capable of activating the methyl groups. The methyl groups of 3,5-dimethyl-4-benzoyl- and 3,5-dimethyl-4-cyano-isoxazoles, and those of 3,5-dimethylisoxazol-4-yl trimethyl ammonium iodide do not undergo condensation even under vigorous conditions.[149] By contrast, 4-nitro-5-methylisoxazoles readily condense with aromatic aldehydes under the mild conditions of boiling in alcohol in the presence of secondary amines.[107,150,151]

A more detailed investigation of the reactivity of methyl groups in nitroisoxazoles was carried out on 3,5-dimethyl-4-nitroisoxazole (**98**).[149] It was found that the methyl group at C-5 (but not at C-3) is highly reactive; besides condensing with aromatic aldehydes and their anils, it reacts with *N,N'*-diarylformamidines and *p*-nitrosodimethylaniline (**98** → **99**). It also undergoes Michael-type reactions with



benzalacetophenone (to yield **100**) and acridine.



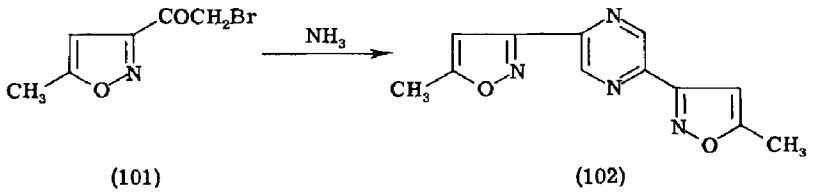
[149] N. K. Kochetkov, S. D. Sokolov, and V. M. Luboshnikova, *Zhur. Obshchei Khim.* **32**, 1778 (1962).
[150] A. Quilico and C. Musante, *Gazz. chim. ital.* **72**, 399 (1942).
[151] C. Musante, *Gazz. chim. ital.* **73**, 355 (1943).

The selective activation of the methyl group in the 5-position is of considerable importance. This may be compared with the preceding activation of the nucleophilic substitution at C-5 by the substituent at C-4 (Section IV,B).

This is in accordance with the foregoing data given (see Sections III and IV,C,1). It seems to be due to incomplete delocalization of double bonds leading to a stronger hyperconjugation with the participation of the hydrogen atoms of the methyl group and possibly to some electron-accepting effect of the nitrogen atom.

F. Miscellaneous Reactions

Among other reactions proceeding with the retention of the heterocyclic nucleus may be noted the synthesis of amino acids of the isoxazole series from isoxazole-5-aldehydes,[152] the successful extension of the Schmidt reaction to 3-acylisoxazoles,[153] and the synthesis of various polycyclic heterocycles, e.g. **101** → **102**, involving the isoxazole nucleus.[154,155]

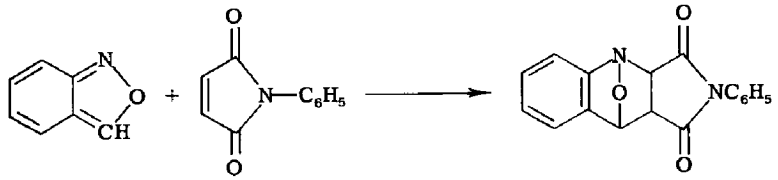


Mention must also be made of an interesting reaction (**103** → **104**) that makes use of the isoxazole nucleus of anthranil as a diene in the reaction with *N*-phenylmaleimide.[156] This instance is of considerable interest, for it has proved impossible to introduce into the diene synthesis other derivatives with a noncondensed isoxazole ring.[157]

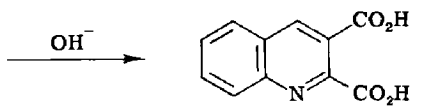
V. Reactions Proceeding with Cleavage of the Isoxazole Ring

Reactions of isoxazole derivatives that take place with the cleavage of the heterocyclic nucleus are as characteristic in this series as the substitution reactions. They are due to the cleavage of the bond

[152] G. Stagno d'Alcontres and R. Scoglio, *Biochim. appl.* **4**, 109 (1957).
[153] S. Palazzo and B. Tornetta, *Ann. chim. (Rome)* **49**, 842 (1959).
[154] L. Giammanco, *Gazz. chim. ital.* **87**, 1139 (1957).
[155] S. V. Sokolov and I. Ya. Postovskii, *Zhur. Obshchei Khim.* **30**, 1781 (1960).
[156] C. D. Nenitzescu, E. Ciorăńescu, and L. Bîrlădeanu, *Comm. acad. rep. populare Romîne* **8**, 775 (1958).
[157] I. I. Grandberg and A. N. Kost, *Zhur. Obshchei Khim.* **29**, 1099 (1959); F. Fariña, *Rev. Real Acad. Ciencias (Madrid)* **45**, 371 (1951).



(103) (104)



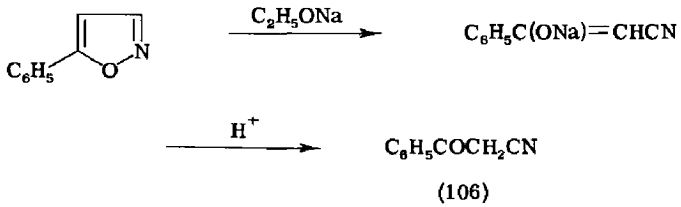
(105)

O—N in the heterocycle and occur extremely readily by the action of nucleophiles and reducing agents.

A. The Opening of the Isoxazole Ring by the Action of Nucleophilic Agents

As already noted, the lability of the isoxazole nucleus toward the action of nucleophilic agents distinguishes this heterocyclic system from those of other azoles and of pyridine. The conditions which lead to ring opening, and the products of ring cleavage are quite varied and depend on the position and the nature of substituents, although it is invariably the N—O bond which is broken.

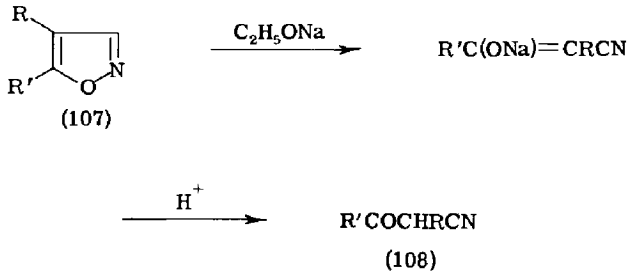
This group of reactions has already been reviewed by Quilico[2] and Barnes.[1] However, the important data recently published make it advisable to reassess the subject. In 1891 Claisen first gave an example of the cleavage of the isoxazole ring: he treated 5-phenylisoxazole with dilute sodium hydroxide or sodium ethylate at room temperature,[158] the reaction involving the cleavage of the O—N bond to yield a β-ketonitrile (**106**).



(106)

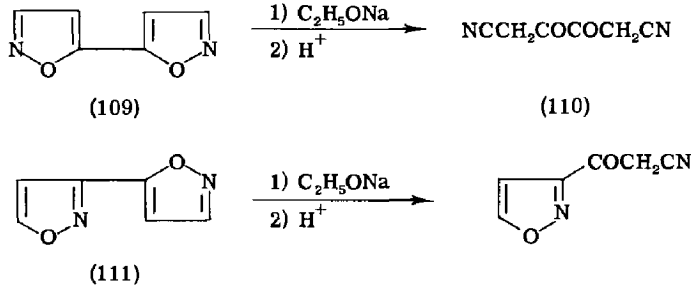
[158] L. Claisen and R. Stock, *Ber. deut. chem. Ges.* **24**, 130 (1891).

Further investigation of the action of sodium ethylate on isoxazole showed that under the same conditions the ring of isoxazole itself is cleaved[125] as well as that of 4- and 5-monosubstituted and 4,5-disubstituted isoxazoles, that is to say, in all isoxazoles unsubstituted at the 3-position, i.e. **107** → **108**.



(107) (108)

In these compounds the following substituents can be present: alkyl,[14,15,21,159-161] alkenyl,[162] aryl,[160] halogen,[106,114] sulfonic acid,[112] amino,[29] hydroxyalkyl,[163] acyl,[164,165] and carboxyl.[24,162,166,167] The cleavages of 5,5′- (**109**) and 3,5′-diisoxazolyl (**111**) proceed similarly; both isoxazole rings are cleaved in the former (**109** → **110**).[35,108]



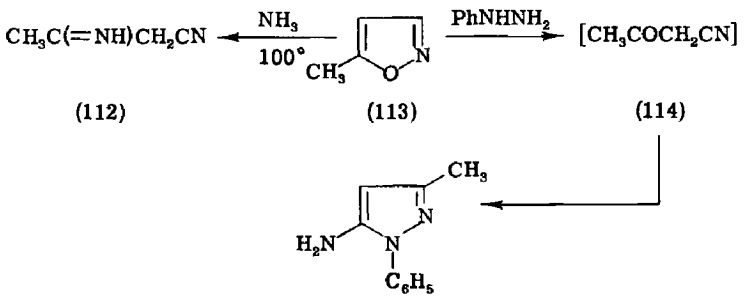
(109) (110) (111)

[159] L. Claisen, *Ber. deut. chem. Ges.* **25**, 1787 (1892).
[160] P. Pino and R. Ercoli, *Rend. ist. lombardo sci. Pt. I* **88**, 378 (1955); *Chem. Abstr.* **50**, 6432 (1956).
[161] R. Justoni, *Rend. ist. lombardo sci. Pt. I* **71**, 407 (1938); *Chem. Abstr.* **34**, 3268 (1940).
[162] A. Quilico and L. Panizzi, *Gazz. chim. ital.* **72**, 458 (1942).
[163] A. Quilico and G. Stagno d'Alcontres, *Gazz. chim. ital.* **79**, 654 (1949).
[164] L. Panizzi, *Gazz. chim. ital.* **72**, 475 (1942).
[165] L. Panizzi, *Gazz. chim. ital.* **77**, 283 (1947).
[166] L. Panizzi, *Gazz. chim. ital.* **73**, 13 (1943).
[167] L. Panizzi, *Gazz. chim. ital.* **77**, 206 (1947).

It is sometimes impossible to isolate the resultant β-ketonitrile derivatives as such as they are unstable and readily polymerize, e.g. cyanoacetone.[159] They are therefore identified as their corresponding arylhydrazones. The simpler alkyl-ω-cyanomethyl ketones are, however, much more stable and their production through the cleavage of 5-alkylisoxazoles has been suggested as a preparative synthetic method.[21]

To cleave the isoxazole ring, good results were also obtained by using other alcoholates[165,168] as well as the recently suggested sodium amide.[27] The latter is, however, hardly to be recommended as a general reagent.

Under more vigorous conditions such as prolonged heating, the degradation of these isoxazoles is also effected by weaker nucleophilic reagents. Thus, 5-methylisoxazole (**113**) on treatment with ammonia is partly converted into cyanoacetoneimine (**112**) and when refluxed with phenylhydrazine yields 1-phenyl-3-methyl-5-aminopyrazole (**115**), in the latter case undoubtedly via the intermediate formation of cyanoacetone (**114**).[169]

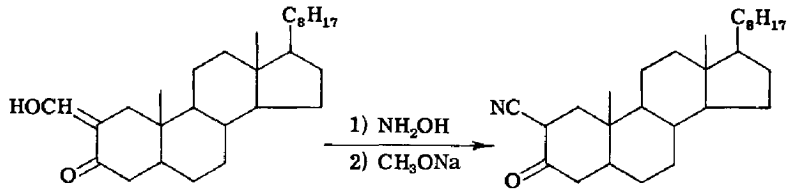


The cleavage of isoxazoles with no substituent in the 3-position by sodium alcoholates has been used analytically to determine the percentage of 5-alkyl- and 5-aryl-isoxazoles in mixtures with their 3-isomers (see, e.g., footnotes 19 and 20).

It has been shown that hydroxymethylene cyclohexanones, in contrast to their cyclopentanone analogs, can be smoothly converted into α-cyanocyclohexanones by the nucleophilic cleavage of the corresponding isoxazoles. This was suggested as a method to distinguish between the cyclohexanones and cyclopentanones.[170] It has also led to the development of a new method for the introduction of a cyano group into ketones which has proved very useful for the synthesis of steroids and related compounds, e.g. **116** → **117**.[168,171,172]

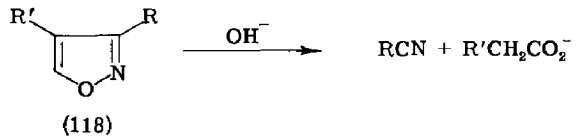
[168] G. V. Kondratyeva, L. F. Kudrjavtseva, and S. I. Zavjalov, *Zhur. Obshchei Khim.* **31**, 3621 (1961).

[169] L. Claisen, *Ber. deut. chem. Ges.* **42**, 59 (1909).



The opening of the isoxazole ring with a substituent at C-3 proceeds differently and the reaction can take various courses depending on the nature of the substituent. Besides sodium ethylate this reaction has been effected with sodium and potassium hydroxides in alcoholic or aqueous media (see, for instance, references 125 and 142).

The first reaction to be investigated was the cleavage of 3-alkyl- and 3-aryl-isoxazoles (**118**: R = CH_3, C_6H_5, R′ = H[125]; R = C_6H_5, R′ = NO_2[173]; R = CH_3, R′ = SO_3H[112]). The cleavage of the N—O bond is accompanied by the cleavage of the bond between C-3 and C-4 to produce nitriles and carboxylic acids, usually isolated as their salts.



In other cases degradation proceeds without the cleavage of a C—C bond in the isoxazole ring but may involve breaking the bond between the substituent at C-3 and the ring. If the 3-substituent is a group that can be eliminated as an anion (as in **119**: X = Cl[46]; CN[142];

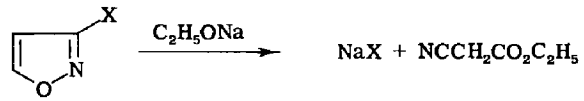
[170] W. S. Johnson and W. E. Shelberg, *J. Am. Chem. Soc.* **67**, 1745 (1945).

[171] W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *J. Am. Chem. Soc.* **69**, 2942 (1947).

[172] F Winternitz, Chr. Menou, and E. Arnal, *Bull. soc. chim. France* p. 505 (1960).

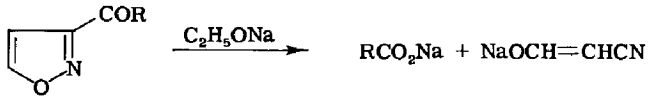
[173] H. Wieland, *Ann.* **328**, 154 (1903).

N_3[174]), the heterocyclic nucleus is converted to cyanoacetic ester (**119** → **120**). Such a reaction occurs very readily, even at room



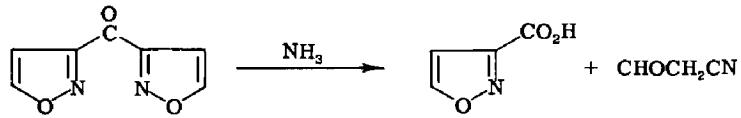
(**119**) (**120**)

temperature, with 3-cyanoisoxazole.[142] When 3-acylisoxazoles (**121**) are heated with sodium ethylate, an acyl cation is eliminated to form the salt of a carboxylic acid and sodium cyanoacetaldehyde (**122**).[142,175,176] The presence of a substituent at the 5-position in



(**121**) (**122**)

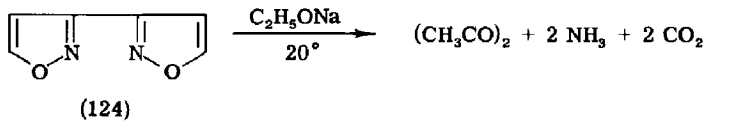
3-acylisoxazoles does not affect the direction of their nucleophilic cleavage but here a β-ketonitrile rather than cyanoacetaldehyde results.[177,178] The literature contains a similar example of the degradation of an isoxazole nucleus (**123**), which proceeds under milder conditions, viz. in ethanolic ammonia.[140]



(**123**)

The only exception is represented by isoxazole-3-carboxylic acid in which the N—O bond is the only one to be broken, other bonds remaining unaffected[162]; hydrolysis of the intermediate (not isolated) gave carbethoxypyruvic acid. Quilico *et al.* reported the peculiar degradation of 3,3′-diisoxazolyl (**124**)[108]: treatment with sodium ethylate even at room temperature yields diacetyl with the evolution

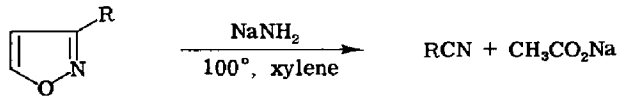
[174] A. Quilico and M. Simonetta, *Gazz. chim. ital.* **76**, 255 (1946); A. Quilico, *ibid.* **61**, 759 (1931).
[175] A. Quilico and M. Freri, *Gazz. chim. ital.* **60**, 172 (1930); *ibid.* **76**, 3 (1946).
[176] A. Quilico and M. Simonetta, *Gazz. chim. ital.* **77**, 586 (1947).
[177] A. Quilico, R. Fusco, and V. Rosnati, *Gazz. chim. ital.* **76**, 30 (1946).
[178] A. Quilico and M. Simonetta, *Gazz. chim. ital.* **76**, 200 (1946).



(**124**)

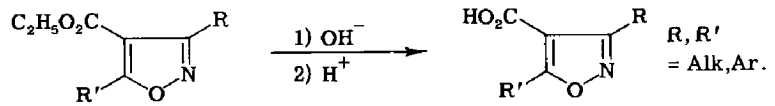
of ammonia and carbon dioxide. The reaction may be supposed to follow the usual scheme (see in following), but diacetyl diimine dicarboxylic acid first loses ammonia by hydrolysis and then undergoes double elimination of carbon dioxide.

Sometimes, for example for analytical purposes, it is convenient to make use of the smooth cleavage of 3-substituted isoxazoles by sodium amide on heating in inert solvents.[27] It is to be noted that, although the reaction occurs in an inert solvent, cleavage of the heterocyclic nucleus is effected rather than a Chichibabin reaction (**125** → **126**).



(**125**) (**126**)

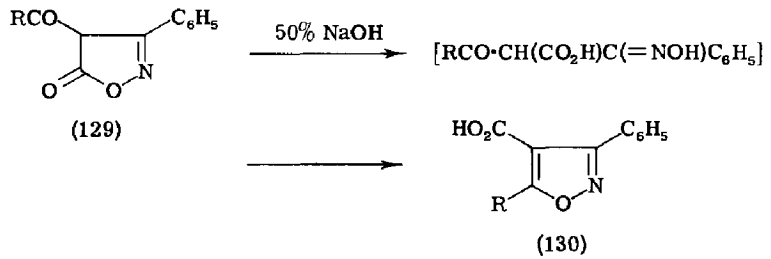
3,5-Disubstituted and trisubstituted isoxazoles are generally stable to alcoholic and aqueous alkali. Such stability of the ring is characteristic both of alkyl-substituted compounds[125,126] and of the esters, nitriles, etc., of isoxazole carboxylic acids,[179-182] for example (**127** → **128**).



(**127**) (**128**)

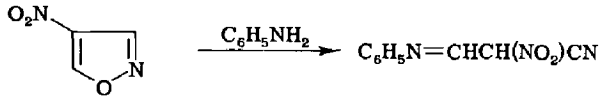
4-Acylisoxazol-5-ones (**129**), which are β-diketones, on being heated in alkaline medium undergo acyl-lactonic rearrangement to form stable isoxazole-4-carboxylic acids (**130**).[132,183]

[179] L. Claisen, *Ann.* **277**, 173 (1893).
[180] A. Quilico and R. Fusco, *Rend. ist. lombardo sci. Pt. I* **69**, 439 (1936); *Chem. Abstr.* **32**, 7454 (1938).
[181] A. Quilico and R. Fusco, *Gazz. chim. ital.* **67**, 589 (1937).
[182] A. Quilico, L. Panizzi, and U. Cavezzuti, *Gazz. chim. ital.* **68**, 625 (1938).
[183] F. Korte and K. Störiko, *Chem. Ber.* **94**, 1956 (1961).



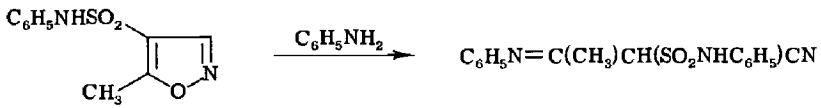
(129) (130)

The introduction of electron-accepting substituents into the isoxazole nucleus sharply increases its lability toward nucleophilic agents. Thus, whereas isoxazole is cleaved by ethanolic alcoholates, its 4-nitro derivative (**131**) requires merely heating with aniline for ring



(131)

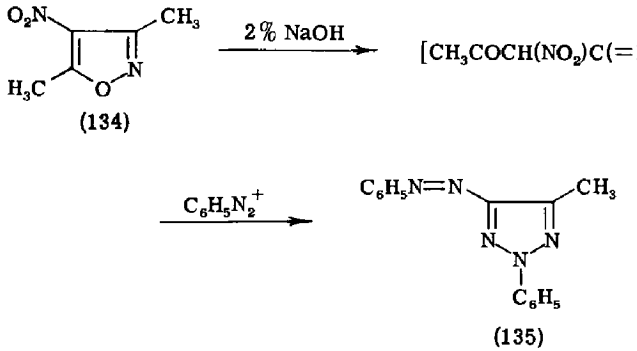
opening.[184] 4-Substituted 5-methylisoxazoles behave similarly[112,150] for example, **132** → **133**.



(132) (133)

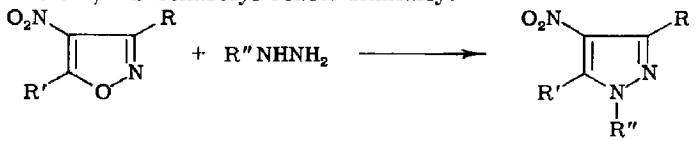
A nitro group in the 4-position markedly increases the instability of the isoxazole ring in alkaline medium. This effect is clearly demonstrated by 3,5-dimethyl-4-nitroisoxazole. Whereas 3,5-dimethylisoxazole is not affected by alkali, its 4-nitro-derivative (**134**) is cleaved by 2% sodium hydroxide. The structure of the product was proved by its conversion into a triazole (**135**) with phenyl diazonium chloride, according to the original authors.[150]

[184] H. S. Hill and W. J. Hale, *Am. Chem. J.* **29**, 253 (1903).



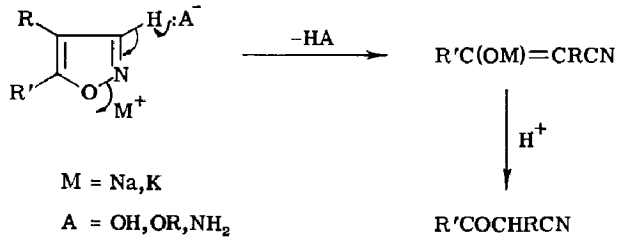
(134) (135)

It has already been mentioned that 5-methylisoxazole is converted into a pyrazole derivative by phenylhydrazine. All 4-nitroisoxazoles undergo this same reaction (**136** → **137**).[102,151,184,185] 5,5′-Dimethyl-4,4′-dinitro-3,3′-diisoxazolyl reacts similarly.[107]



(136) (137)

The mechanism of the nucleophilic cleavage of the isoxazole nucleus can now be considered as well understood. The first stage of almost all variants of this reaction consists in the removal of the proton by the nucleophile from the unsubstituted carbon atom with the lowest electron density of the isoxazole ring, usually C-3 or C-5. Neutralization of the negative charge of the resulting isoxazolyl anion causes the

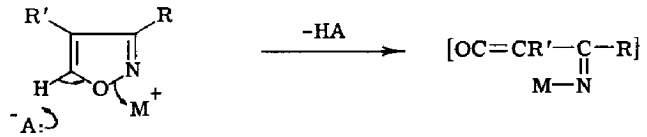


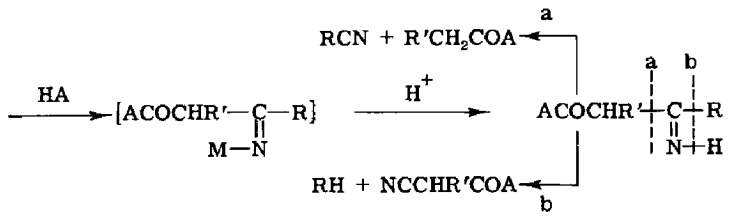
(3)

[185] C. Musante and A. Stener, *Gazz. chim. ital.* **89**, 1579 (1959).

rupture of the N—O bond. Thus, the cleavage of the 4,5-disubstituted isoxazole may be shown in Eq. (3).[2,186]

When 3,4-disubstituted isoxazoles are cleaved it is the proton at C-5 that is removed [Eq. (4)].[2]

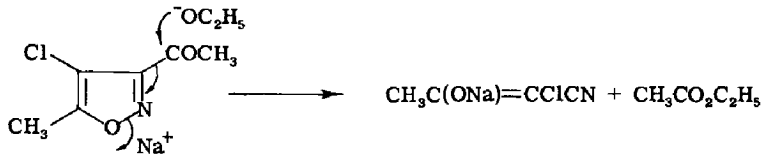




(4)

The monoimine of the β-diketo-compound is either stable (A = OC_2H_5, R = CO_2H, R′ = H, cf. footnote 162) or it disintegrates. The degradation may proceed by a path similar to the acid degradation of β-diketones with the rupture of the C—C bond (route a) and the formation of a nitrile (if R = Alk, Ar). When the group R shows a strong tendency to form an anion (R = CN, N_3, Cl) the degradation follows route b to a β-ketonitrile.

The cleavage of 3-acylisoxazoles proceeds differently, the nucleophilic agent attacking the carbon atom of the carbonyl group, for example (**138** → **139**).[177]



(138) (139)

The preceding mechanism of the nucleophilic opening of the isoxazole ring is in accordance with the kinetic evidence of Pino

[186] G. Speroni and P. Pino, *Proc. Intern. Congr. Pure and Appl. Chem., 11th Congr., London* **2**, 311 (1947).

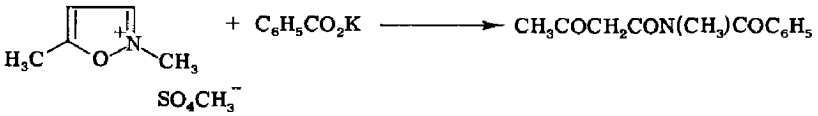
et al.[116,160,187] These authors conclude that cleavage is a first-order reaction with respect to the nucleophilic anion. Of interest are their comparative data on the reaction rate for differently substituted isoxazoles:[160]

	Isoxazole	4-Methyl~	5-Methyl~	3-Methyl~
$K \times 10^4$ [l./(moles)(sec)]	4.5	3.1	1.4	0.1

It is seen from these figures that the introduction in the isoxazole nucleus of the electron-donating methyl group into position 4 results in the decrease of the reaction rate constant. A converse effect is found with 4-bromoisoxazole which cleaves 100 times faster than does isoxazole because of the negative inductive effect of the bromine atom.[116] The introduction of a methyl group into the 3- or 5-positions of the isoxazole ring affects the cleavage reaction rate even more. This is because the methyl group at C-3 or C-5 replaces in the isoxazole ring one of the hydrogen atoms that can be removed as a proton by the nucleophile and somewhat increases the over-all electron density in the nucleus. One should note the difference in the rate constants for 5- and 3-methylisoxazoles, indicating a stronger electron-accepting effect of the nitrogen hetero atom at C-3 as compared with its influence at C-5.

Quaternization of the isoxazole nitrogen atom makes the ring particularly susceptible toward nucleophilic attack; there is a certain analogy here with pyridine. The cleavage of the ring proceeds extremely readily in quaternary salts of isoxazole, even occurring by the action of such weak nucleophilic agents as the anions of carboxylic acids.

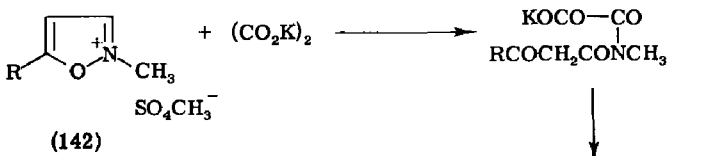
In 1909, Claisen described the first such reaction. Treating 2,5-dimethylisoxazolium methosulfate (**140**) with potassium benzoate in aqueous media he obtained the *N*-methyl-*N*-benzoyl amide (**141**) of acetoacetic acid.[169]



(140) (141)

[187] P. Pino, A. Scartabelli, and E. Lombardi, *Rend. ist. lombardo sci. Pt. I* **87**, 229 (1954); *Chem. Abstr.* **49**, 15397 (1955).

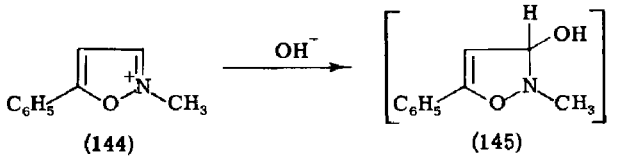
Later this interesting reaction was extended to other examples by Mumm *et al.* and it proved to be of synthetic value, particularly for various heterocyclic systems,[188-192] for example, **142** → **143**.



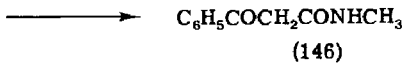
(142)

(143)

The cleavage proceeds under extremely mild conditions in aqueous solution at room temperature and can therefore be used for complicated syntheses. The mechanism of this reaction proved to be very complicated and has been elucidated only recently. The ring opening of quaternary salts of trisubstituted isoxazoles by nucleophiles proceeds under similar conditions, and the mechanism of this reaction was extensively studied by Kohler *et al.*[193-195] The authors claimed that the reaction consists of addition of the anion either at C-3 of the ring (if this is unsubstituted) or at C-5 (with 3,4,5-tri-



(144) (145)



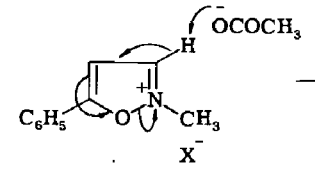
(146)

[188] O. Mumm and G. Münchmeyer, *Ber. deut. chem. Ges.* **43**, 3335 (1910).
[189] O. Mumm and C. Bergell, *Ber. deut. chem. Ges.* **45**, 3040 (1912).
[190] O. Mumm and C. Bergell, *Ber. deut. chem. Ges.* **45**, 3149 (1912).
[191] A. Knust and O. Mumm, *Ber. deut. chem. Ges.* **50**, 563 (1917).
[192] O. Mumm and H. Harnhardt, *Ber. deut. chem. Ges.* **70B**, 1930 (1937).
[193] E. P. Kohler and A. H. Blatt, *J. Am. Chem. Soc.* **50**, 1217 (1928).
[194] E. P. Kohler and N. K. Richtmeyer, *J. Am. Chem. Soc.* **50**, 3093 (1928).
[195] E. P. Kohler and W. F. Bruce, *J. Am. Chem. Soc.* **53**, 644 (1931).

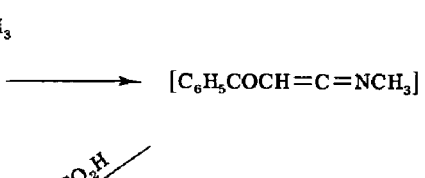
substituted quaternary salts) followed by the degradation of the isoxazoline formed, for example, **144** → **145** → **146**. Although the structure of the resulting product was assigned correctly, the suggested structure of the intermediate compound was not well founded.

King and Durst have recently found the ring opening of trisubstituted isoxazole quaternary salts to result in the formation of 1,3-(2*H*)-oxazine derivatives.[195a]

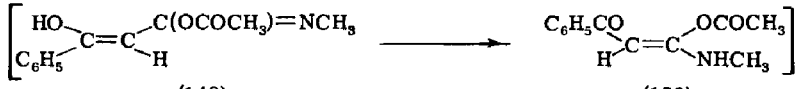
Only in 1961 did Woodward and Olofson succeed in elucidating the true mechanism of this interesting reaction by making an extensive use of spectroscopic methods.[196] The difficulty was that the reaction proceeds in many stages. The isomeric compounds formed thereby are extremely labile, readily interconvertible, and can be identified only spectroscopically. The authors found that the attack by the anion eliminates the proton at C-3 (**147**); subsequent cleavage of the N—O bond yields a β-oxoketene imine (**148**) whose formation was established for the first time. The oxoketene imine spontaneously adds acetic acid and is converted via two intermediates (**149**, **150**) to an enol acetate (**151**) whose structure was determined by UV spectra. Finally the enol acetate readily yields the *N*-acyl derivative (**152**).



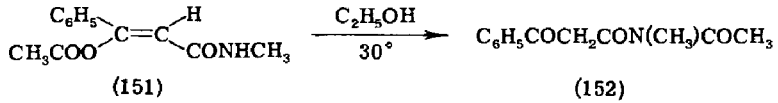
(147)



(148)



(149) (150)



(151) (152)

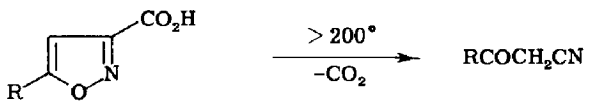
[195a] J. F. King and T. Durst, *Can. J. Chem.* **40**, 882 (1962).
[196] R. B. Woodward and R. Olofson, *J. Am. Chem. Soc.* **83**, 1007 (1961).

The early stages of the reaction of the quaternary salt can be regarded as proceeding in a manner exactly analogous to that by which the isoxazoles themselves are degraded, the β-oxoketene imine structure (**148**) being one mesomeric form of a compound which could alternatively be formulated as a nitrilium betaine. However, by contrast with the products from the isoxazoles (i.e., enolates of β-ketonitriles), this is electrically neutral and susceptible to further nucleophilic attack.

The smooth conversion of the enol acetate (**151**) into an *N*-acyl derivative (**152**) under extremely mild conditions points to the high acylating capacity of these esters. This cleavage of isoxazolium salts is also caused by other anions of carboxylic acids, and thus they can be readily converted to reactive enol esters. A very convenient and specific synthesis of peptides due to Woodward *et al.*[113] is based on this reaction.

B. Decarboxylation of Isoxazole-3-carboxylic Acids

Decarboxylation of isoxazole-3-carboxylic acids is related to the nucleophilic cleavage of the isoxazole ring as far as the nature of the reaction products is concerned. It occurs at temperatures above 200°C and is accompanied by the cleavage of the nitrogen-oxygen bond of the heterocyclic ring to yield a β-ketonitrile. It was first reported by Claisen with 5-methyl- and 5-phenyl-isoxazole-3-carboxylic acids (**153** → **154**).[197] Under the reaction conditions, β-ketonitriles condense



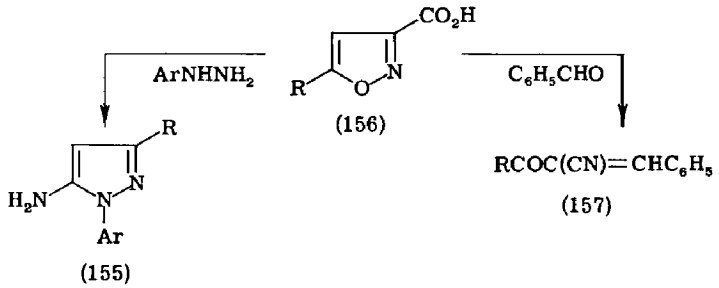
(**153**) (**154**)

to form polymers and the individual reaction product can be isolated in a low yield only if R is an aryl group. This reaction was later extended to other 5-arylisoxazole-3-carboxylic acids,[198,199] including the derivatives of diisoxazolyls,[198] the products having been identified as arylhydrazones or by converting the ketonitriles into the corresponding pyrazoles.

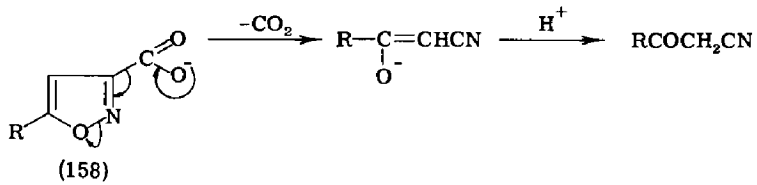
Attempts have been made, of course, to find milder conditions for

[197] L. Claisen, *Ber. deut. chem. Ges.* **24**, 3900 (1891).
[198] A. Quilico and C. Musante, *Gazz. chim. ital.* **70**, 676 (1940).
[199] S. Fatutta and M. Balestra, *Gazz. chim. ital.* **88**, 899 (1958).

this decarboxylation. In 1948, Cusmano and Tiberio[200] found that the addition of copper powder to the acid solution in aqueous ammonia raises the yield of β-ketonitrile. Increased yields can also be obtained by decarboxylation in the presence of reagents which condense with the β-ketonitrile yielding a more stable compound. The use of arylhydrazines has thus enabled the preparation of 5-aminopyrazoles (**155**) in 80–100% yield,[201,202] whereas benzaldehyde allowed the use of a considerably lower reaction temperature. For instance, with R = *p*-nitrophenyl the reaction (**156** → **157**) occurs even in boiling alcohol.[203]



The mechanism of the decarboxylation of isoxazole-3-carboxylic acids has not yet been specially studied, but the available experimental evidence allows some suggestions to be made. It seems that on heating isoxazole carboxylic acids in solution, or in the presence of arylhydrazines, it is the acid anion (**158**) formed which is being de-



(**158**)

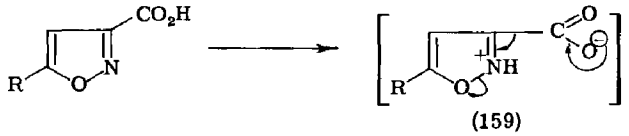
carboxylated and the degradation then follows the path described in the foregoing for the nucleophilic cleavage of 5-substituted isoxazoles (see Section V,A).

For isoxazole-3-carboxylic acids with a 4-acyl or 4-alkoxycarbonyl

[200] S. Cusmano and T. Tiberio, *Gazz. chim. ital.* **78**, 896 (1948).
[201] S. Cusmano, *Gazz. chim. ital.* **69**, 594, 621 (1939).
[202] C. Musante and S. Fatutta, *Gazz. chim. ital.* **88**, 879 (1958).
[203] S. Cusmano and S. Giambrone, *Gazz. chim. ital.* **80**, 702 (1950).

substituent, such a degradation is considerably facilitated. It even takes place under the conditions of alkaline hydrolysis of the corresponding esters.[204] On the other hand, acids without such a group at C-4 are stable under these conditions.[153]

Decarboxylation of crystalline isoxazole-3-carboxylic acids appears to proceed by another mechanism,[197,198] probably with formation of a zwitterion (**159**) which reacts as in the case of picolinic acid de-



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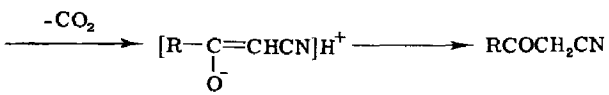
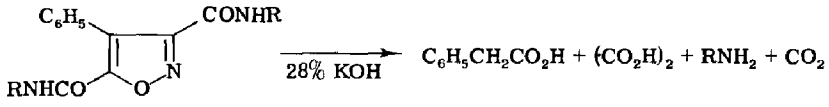


carboxylation.[205] As isoxazoles are weak bases, this process requires higher temperatures. Heating isoxazole-3,5-dicarboxylic amides (**160**) results in complete destruction of the isoxazole ring (**160** → **161**).[78]



(160) (161)

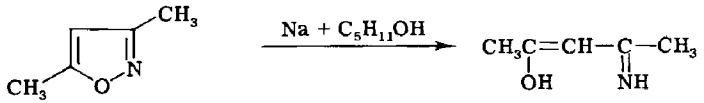
C. Reductive Cleavage of Isoxazoles and of Their Hydrogenated Derivatives

The reduction of isoxazoles is often rather peculiar and its course depends on the nature both of the isoxazole and of the reducing agent. Together with a normal reduction of groupings in the side chain, cleavage of the nitrogen-oxygen bond of the heterocyclic nucleus often occurs.

Hydrogenolysis of the ring of di- and tetra-hydroisoxazole derivatives proceeds, of course, more readily than in the case of the aromatic system of isoxazole. These two reactions are discussed separately below.

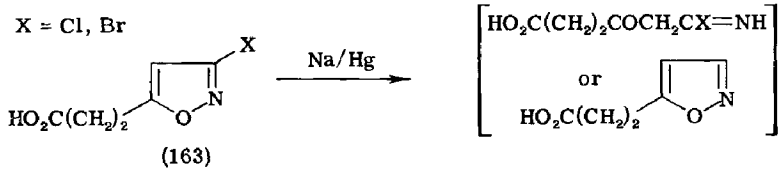
1. *Reductive Cleavage of Isoxazole Derivatives*

Claisen first observed cleavage of the isoxazole ring by the action of reducing agents. He isolated acetylacetone imine (**162**) by reducing 3,5-dimethylisoxazole with sodium in amyl alcohol or moist ether.[197]

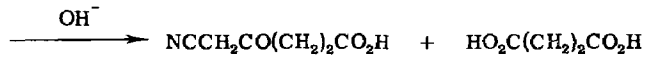


(162)

Similar results were obtained on reduction of 3,4,5-trimethylisoxazole.[127] Further examples of such a cleavage were found later. Thus, β-(3-halogenoisoxazol-5-yl) propionic acids (**163**) on treatment with sodium amalgam give a mixture of δ-cyano-γ-ketovaleric and succinic acids (**163** → **164**).[12] The reaction can be interpreted as a result of



(163)



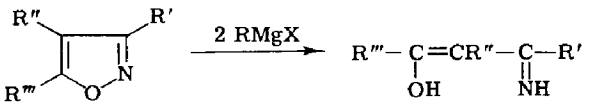
(164)

direct reductive cleavage of the halogenoisoxazole. At the same time one should not exclude the possibility of a nucleophilic cleavage of the ring after preliminary dehalogenation. Therefore the mechanism of the reaction needs further investigation.

The degradation which occurs on reduction with the alkali metals involve a mechanism that is considered to be firmly established[206,207] and in the isoxazole series appears to proceed according to the usual scheme.

A related cleavage reaction (**165** → **166**) occurs on the treatment of isoxazoles with organomagnesium compounds.[126,194,208] This reaction considerably hinders the use of the Grignard reaction in the isoxazole series (see Section IV,D); in it the activity of the organo-

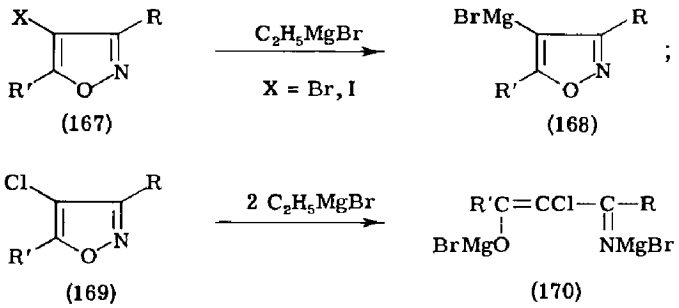
[204] C. Musante, *Gazz. chim. ital.* **69**, 523 (1939).
[205] N. H. Cantwell and E. V. Brown, *J. Am. Chem. Soc.* **75**, 4466 (1953).
[206] J. H. Brewster, *J. Am. Chem. Soc.* **76**, 6361 (1954).
[207] G. J. Hoijtink, *Rec. trav. chim.* **76**, 885 (1957).
[208] N. K. Kochetkov and S. D. Sokolov, *Zhur. Obshchei Khim.* **33**, in press (1963).



(165) (166)

magnesium compound decreases in the sequence $C_2H_5MgBr > CH_3MgI > C_6H_5MgBr$.

The difference in the behavior of various 4-halogenoisoxazoles on reductive cleavage by organomagnesium compounds is of interest. Thus iodo, and to a lesser extent bromo compounds, undergo exchange reactions (**167**, X = Br, I → **168**) on treatment with ethylmagnesium bromide to yield isoxazole organomagnesium compounds (see Section IV,D), whereas chloro derivatives (**169**) suffer reductive cleavage which produces α-chloro-β-diketone monoimines (**170**).[208] With chloroisoxazoles a similar result is obtained by treatment with magnesium in the presence of ethyl bromide or dibromoethane.[8,208]

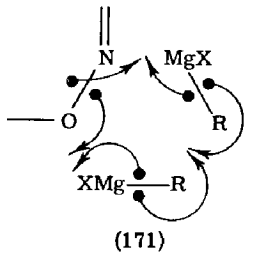


(167) (168)

(169) (170)

The cleavage of the isoxazole ring by organomagnesium compounds may proceed by either one or both of two alternative mechanisms. Magnesium subhalides produced during the associated reaction may act as reducing agents as proved in specific cases.[208] Another possibility is that the reduction involves a six-membered cyclic complex (**171**).

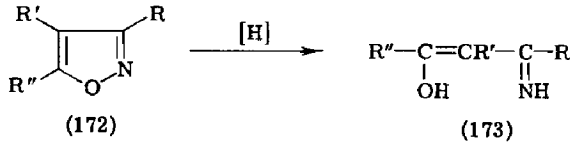
Thus, all the foregoing reactions involving reductive cleavage of the nitrogen-oxygen bond of the isoxazole ring (except for the last example) seem to proceed according to a single mechanism (cf. footnote 206) with the first stage comprising the addition of one or two electrons. Reducing agents which act by other mechanisms probably do not, in general, destroy the isoxazole ring. Thus, lithium aluminum



(171)

hydride has been successfully used to synthesize carbinols from acylisoxazoles,[62,209] secondary amines from anils,[210] and isoxazolyl hydrazines from hydrazones.[211] Reduction with zinc in ethanol or acetic acid also does not affect the heterocyclic ring.[19,62]

Another group of reactions with the predominant cleavage of the ring comprises catalytic hydrogenation of isoxazole derivatives and has been investigated only recently. The most commonly used catalyst has been Raney nickel,[46,116,210,212-214] but use has sometimes been made of platinum catalysts.[46,213] Hydrogenolysis of the O—N bond (**172** → **173**) occurs in isoxazole, its homologs,[116,212] and their functional derivatives, for example, isoxazole carboxylic acids[212] and 5-aminoisoxazoles.[210,213,214]



(172) (173)

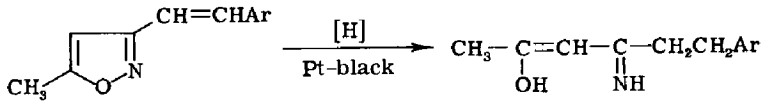
The monoimines of the substituted β-diketones formed can usually be isolated but sometimes they undergo further reactions. Thus, 5-substituted 3-chloroisoxazoles yield β-ketonitriles,[46] and hydrogenation of 5-acylaminoisoxazoles (**174**) is a general method of synthesizing 4-hydroxypyrimidines (**175**).[213,214]

One should note the increased stability of the isoxazole ring in styrylisoxazoles toward reduction. No hydrogenolysis of the O—N

[209] P. N. Craig and M. P. Olmsted, *J. Org. Chem.* **22**, 559 (1957).
[210] H. Kano and Y. Makisumi, *Yakugaku Zasshi* **76**, 1311 (1956).
[211] T. S. Gardner, J. Lee, and E. Wenis, U. S. Patent 2,908,688 (13/10/1959).
[212] G. Stagno d'Alcontres, *Gazz. chim. ital.* **80**, 441 (1950).
[213] G. Shaw and G. Sugowdz, *Nature* **172**, 955 (1953); *J. Chem. Soc.* p. 665 (1954).
[214] H. Kano and Y. Makisumi, *Pharm. Bull. (Tokyo)* **3**, 270 (1955); *Chem. Abstr.* **50**, 12061 (1956).

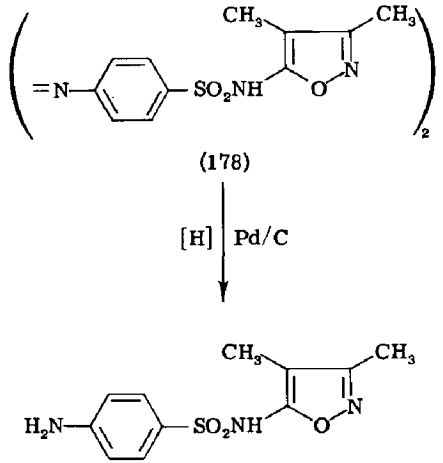
(174) (175)

bond is observed in these compounds either on reaction with sodium in moist ether or on catalytic hydrogenation with Raney nickel. The reaction **176** → **177** could be effected only on hydrogenation catalyzed by platinum black.[148]



(176) (177)

In almost all known cases of the catalytic hydrogenation of isoxazole derivatives the reaction is accompanied by the hydrogenolysis of the ring. The only example of catalytic reduction of a functional group not affecting the heterocyclic system seems to be the reduction of the azo group in **178** with a palladium catalyst during the synthesis of the sulfonamide drug, hentrizine (**179**).[215]



(178) (179)

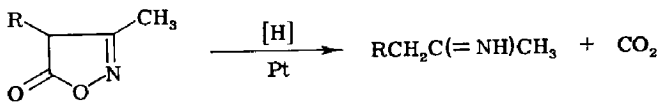
[215] W. Guex, R. Schläpfer, and H. Spiegelberg, Swiss. Patent 341156 (14/11/1959).

Conditions for the hydrogenation of the double bonds of the isoxazole ring leading to dihydro and tetrahydro derivatives are as yet unknown.

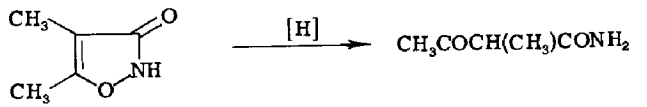
2. *Reductive Cleavage of Isoxazolines and Isoxazolidines*

As already mentioned, on passing from the aromatic system of isoxazoles to the nonaromatic ones of isoxazolines and isoxazolidines, the N—O bond becomes more labile. In these compounds the ring is extremely readily cleaved. Many such reactions are useful to determine the structure of reduced isoxazole derivatives and are also of preparative value.

Under the conditions used for the reductive cleavage of the O—N bond in isoxazoles, a similar reaction readily occurs with isoxazolines, e.g. on treatment with organomagnesium compounds[193,216,217] and on catalytic hydrogenation.[218] Hydrogenolysis of the O—N bond (**180** → **181**; **182** → **183**) was used to elucidate the structure of isoxazolones from β-ketoesters.[32]



(180) (181)

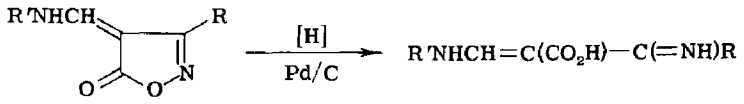


(182) (183)

Shaw concluded that hydrogenation of 3-alkyl-4-aminomethylene isoxazol-5-ones (**184**) in the presence of palladium catalyst resulted in the saturation of either the endocyclic double carbon-nitrogen bond or the exocyclic double C=C bond with the retention of the heterocyclic nitrogen-oxygen bond.[219] Recent data reported by Kochetkov *et al.* on the properties, and in particular on hydrogenation, of isoxazolid-5-ones[220] indicate, however, that Shaw had probably ob-

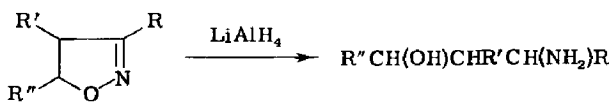
[216] E. P. Kohler and G. R. Barrett, *J. Am. Chem. Soc.* **46**, 2105 (1924).
[217] E. P. Kohler and N. K. Richtmeyer, *J. Am. Chem. Soc.* **52**, 2038 (1930).
[218] L. Panizzi, *Gazz. chim. ital.* **76**, 44 (1946).
[219] G. Shaw, *J. Chem. Soc.* p. 720 (1950); *ibid.* p. 1017 (1951).
[220] N. K. Kochetkov, R. M. Khomutov, E. I. Budowsky, M. Ja. Karpeysky, and E. S. Severin, *Zhur. Obshchei Khim.* **29**, 4069 (1959).

tained β-ketoacid imines (**185**). Some reactions of the products[221] are in accord with this suggestion.



(184) (185)

The isoxazoline ring is also readily cleaved by such reducing agents as do not affect the isoxazole ring. Thus, for example, the treatment of isoxazolines (**186**) with $LiAlH_4$ proceeds with a smooth cleavage of the heterocyclic ring to form substituted 3-amino-propan-1-ols (**187**),[53,54,222] whereas isoxazoles are stable under these conditions.

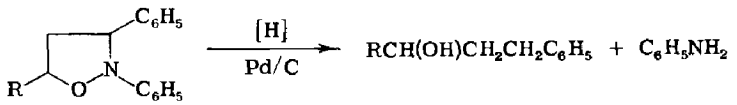


(186) (187)

This reaction is widely used to determine the structure of Δ^2-isoxazolines.[70]

Boiling hydriodic acid also degrades the isoxazoline ring[67,222] but does not affect that of isoxazole.[60,127]

The isoxazolidine ring is also readily cleaved by various reducing agents. For example, the degradation **188** → **189** proceeds smoothly



(188) (189)

on catalytic hydrogenation.[77] The high lability of the nitrogen-oxygen bond in isoxazolidines is seen from the mild conditions required for its reductive cleavage by lithium aluminum hydride[76] and even zinc in acetic acid.[74]

VI. The Action of Oxidizing Agents on Isoxazoles and Isoxazolines

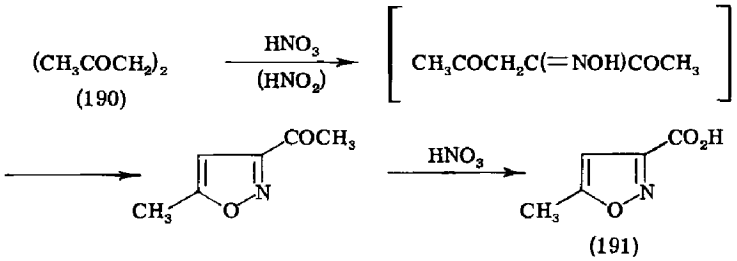
The action of oxidizing agents on isoxazoles fully confirms the aromaticity of this heterocyclic system and is widely used to prepare

[221] G. Shaw, *J. Chem. Soc.* p. 3428 (1952).
[222] G. W. Perold and F. V. K. von Reiche, *J. Am. Chem. Soc.* **79**, 465 (1957).

various derivatives. The isoxazole ring is stable to many oxidizing agents, including strong ones, but this does not apply to reaction in alkaline media.

Oxidizing agents often react with isoxazoline derivatives to dehydrogenate the ring forming an isoxazole system. Mixed chromic and sulfuric acid enables the preparation of isoxazole carboxylic acids by oxidation of such compounds as alkenyl isoxazoles,[141,162] isoxazole carbinols[121,163] and ketones,[177,223] and 4-chloromethylisoxazoles.[121] Chromic anhydride in acetic acid oxidizes the isopropenyl[60] and carbinol[62,122] groups into ketones and dehydrogenates 3,5-diaryl-2-isoxazolines to the corresponding isoxazoles.[51,64] An important method of determining the structure of 2-isoxazolines (see, for example, footnotes 224, 225) is based on this reaction.

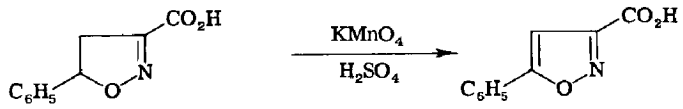
3-Acetylisoxazoles are converted to carboxylic acids by boiling with dilute nitric acid.[226,227] This method allowed the development of a one-stage preparative method for 5-methylisoxazole-3-carboxylic acid (**191**) starting with acetonylacetone (**190**).[211]



(190) (191)

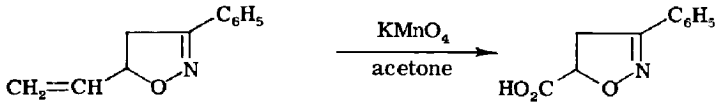
The stability of the heterocyclic ring toward oxidation by permanganate depends on the experimental conditions. In acid media the ring is not cleaved, and acetylisoxazoles are readily prepared from isopropenyl derivatives.[10,141,228] 2-Isoxazolines are dehydrogenated into isoxazoles (cf. **192** → **193**).[65] The stability of the heterocyclic ring is also observed when this oxidation is carried out in acetone solution. It is of interest that this method allows the preparation both of

[223] A. Quilico and G. Speroni, *Gazz. chim. ital.* **70**, 779 (1940).
[224] R. P. Barnes and F. E. Chigbo, *J. Org. Chem.* **23**, 1777 (1958).
[225] G. Stagno d'Alcontres and G. Lo Vecchio, *Gazz. chim. ital.* **90**, 347 (1960).
[226] T. Ajello and C. Petronici, *Gazz. chim. ital.* **72**, 333 (1942).
[227] S. Cusmano, *Gazz. chim. ital.* **78**, 764 (1948).
[228] C. Musante, *Gazz. chim. ital.* **71**, 172 (1941).



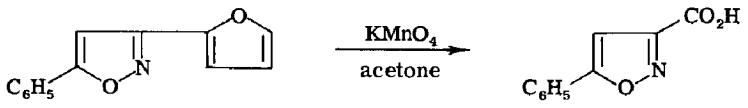
(192) (193)

isoxazole carboxylic acids[60,150,229] and of 2-isoxazoline carboxylic acids (e.g. **194**)[66,68] from unsaturated compounds. If furylisoxazoles are



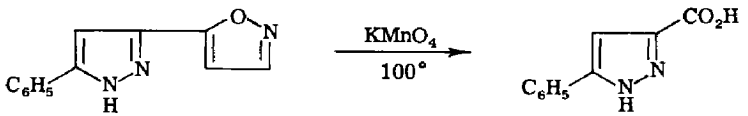
(194)

treated under the same conditions only the furan ring undergoes oxidation (cf. **195** → **196**).[230]



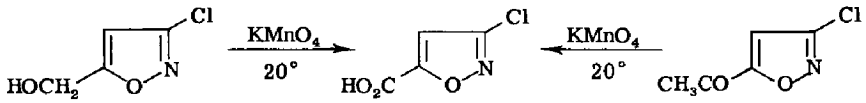
(195) (196)

Heating isoxazole derivatives with aqueous-alkaline permanganate leads to a complete degradation of the heterocycle. With arylisoxazoles this results in readily identifiable aromatic acids, from which can be deduced the orientation of electrophilic substitution reactions.[104,105,117] Also, the stability of various heterocycles can be compared. Thus, under these reaction conditions, the pyrazole ring is more stable than that of isoxazole (cf. **197** → **198**).[230]



(197) (198)

Recently, the successful oxidation with alkaline permanganate of 3-chloro-5-hydroxymethylisoxazole (**199**) and 3-chloro-5-acetylisoxazole (**201**) to the acid (**200**) without cleavage of the heterocyclic ring has been reported, the reaction being carried out at room temperature.[46]



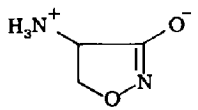
(199) (200) (201)

Isoxazole derivatives are stable toward peracids[231,232] but can be ozonolyzed. This, as is well known, enabled the *O*-benzoyloximes of α-diketones with a well established configuration to be obtained, which were used to investigate the Beckmann rearrangement mechanism.[233,234]

VII. Biologically Active Derivatives of the Isoxazole Series

The extensive investigation of the biological activity of organic compounds that is so characteristic of the last few decades, has also revealed active compounds in the isoxazole series. The main advances have been achieved in recent years.

Biologically, the most important compound of this series proved to be the antituberculosis antibiotic, cycloserine or 4-aminoisoxazolid-3-one (**202**). After this compound had been isolated and its structure determined,[235] numerous studies dealing with its chemistry, biochemistry, and biological activity appeared.



(202)

At present, several syntheses of cycloserine are known, and a number of its analogs have been prepared. These investigations have been reviewed recently.[236]

[229] G. Stagno d'Alcontres and G. de Giacomo, *Atti soc. peloritana sci. fis. mat. e nat.* **5**, 169 (1958–59); *Chem. Abstr.* **54**, 19646 (1960).
[230] C. Musante and R. Berretti, *Gazz. chim. ital.* **79**, 683 (1949).
[231] M. M. Botwinnik and N. I. Gawrilow, *J. prakt. Chem.* **148**, 170 (1937).
[232] C. Musante, *Gazz. chim. ital.* **71**, 553 (1941)
[233] I. Meisenheimer, *Ber. deut. chem. Ges.* **54**, 3206 (1921).
[234] I. Meisenheimer and H. Lange, *Ber. deut. chem. Ges.* **57**, 282 (1924).
[235] K. Folkers *et al.*, *J. Am. Chem. Soc.* **77**, 2344 (1955); P. H. Hidy *et al.*, *J. Am. Chem. Soc.* **77**, 2345 (1955).
[236] N. K. Kochetkov, *Österr. Chemiker-Ztg.* **62**, 276 (1961).

Some hydroxamic acids of the isoxazole series also display a marked antituberculosis activity.[237] The penicillin derivatives, acylated with isoxazole carboxylic acids possess an antibacterial activity similar to that of penicillin, against resistant species.[238] Among other isoxazole derivatives possessing activity one should especially mention the sulfonamides of this series,[215,239] and 4-hydroxyiminoisoxazol-5-ones.[240]

Isoxazole derivatives involve also substances with analgesic and local anaesthetic activity,[241] though nothing is yet known of their wide applications. The hydrazides of isoxazole carboxylic acids are of great interest. Thus, the hydrazide of 5-methylisoxazole-3-carboxylic acid displays a high antileprous activity[242] and the corresponding benzyl hydrazide, known as Marplane (R05-0831) is a strong inhibitor of monoaminoxidase and is being used in psychotherapy[243] and in treatment of angina pectoris.[244] Inhibiting action to aminoxidase has also been noted with other hydrazides of this series.[211,245]

Quite recently great attention has been focused on steroids involving an isoxazole ring in the 2,3-position because of their anabolic activity.[246,247]

[237] C. Caradonna and M. L. Stein, *Farmaco (Pavia) Ed. sci.* **15**, 647 (1960).
[238] F. P. Doyle and J. H. C. Nayler, U. S. Patent 2,996,501 (10/4/1961).
[239] I. Satoda, T. Fukui, and K. Mori, *Yakugaku Zasshi* **79**, 961 (1959).
[240] C. Caradonna, M. L. Stein, and M. Ikram, *Ann. chim. (Rome)* **49**, 2083 (1959).
[241] M. Matter and H. Gerber, U. S. Patent 3,007,936 (29/6/1959).
[242] T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.* **26**, 1514 (1961).
[243] L. O. Randall and R. E. Bagdon, *Ann. N. Y. Acad. Sci.* **80**, 626 (1959).
[244] T. Winsor and P. Zarco, *Angiology* **11**, 67 (1960); *Chem. Abstr.* **54**, 12359 (1960).
[245] C. Bracci Torsi and M. Vuat, *Gazz. chim. ital.* **91**, 1461 (1961).
[246] R. O. Clinton, A. J. Manson, F. W. Stonner, R. G. Christiansen, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Org. Chem.* **26**, 279 (1961).
[247] E. Marchetti and P. Donini, *Gazz. chim. ital.* **91**, 1133 (1961).

Author Index

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